REMARKS

By this amendment, claims 27, 28, 35, and 38 have been amended, claims 63-64 have been added, and claims 29-34 and 39-40 have been cancelled without prejudice. The amendments to the claims are supported in all cases by the specification, e.g., at page 24, and no new matter has been added. Claims 41-62 stand withdrawn from consideration, and thus, claims 27-28, 35-38, and 63-64 are currently under examination in the present application. For the reasons set forth below, Applicants submit that the present amendments and arguments place this application in condition for immediate allowance.

As an initial matter, Applicants wish to thank the Examiner for granting the recent Interview with Applicants' counsel. By the present amendments, Applicants have now amended the claims of the present application in the manner suggested by the Examiner during the Interview of October 5, 2010, such that the claims are more clearly directed toward the elected combination of an antipsychotic or an antidepressant and an antagonist and/or inverse agonist of the histamine H_3 receptor, namely olanzapine and 3-(4-chlorophenyl)propyl-3-piperodinopropyl ether (BF2.649) or pharmaceutically-acceptable salts thereof. Furthermore, as discussed below and also in accordance with the Examiner's suggestions during the Interview, Applicants are hereby submitting a Declaration of Jean-Charles Schwartz pursuant to 37 C.F.R. §1.132 as further evidence of the unexpected and synergistic results which are achieved by the present invention and are reflected in the claims of the present application, as amended.

Before discussing those results, however, in the Office Action dated April 12, 2010, the Examiner maintained a provisional rejection of claims 27-33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25-28 of co-pending U.S. Application No. 11/815,736. In particular, the Examiner continued to assert that claims 25-28 of the co-pending application are directed to a composition comprised of 3-(4-chlorophenyl)propyl-3-piperodinopropyl ether (hydrochloride salt) and that claims 27-33 of the present application are drawn to the same invention. Without further addressing the merits of the Examiner's assertions, Applicants are submitting herewith a terminal disclaimer pursuant to 37 C.F.R. 1.321 and, accordingly, Applicants thus respectfully submit that the Examiner's obviousness-type double patenting rejection should be withdrawn.

In the Office Action, the Examiner also maintained a rejection of claims 27-33 and 35-38 under 35 U.S.C. §103(a) as being unpatentable over International Patent Application Publication No. WO 00/74784 ("Todd") and U.S. Patent No. 7,138,416 ("Schwartz"). In particular, the Examiner continued to assert that, although neither Todd nor Schwartz teaches a specific combination of olanzapine and 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, it would have been obvious to formulate a composition comprised of olanzapine and 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether because Schwartz teaches that 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether is effective in treating obesity and cognitive deficits, and because Todd teaches that compositions comprised of olanzapine and H_2 histamine antagonists are effective in reducing weight gain. Furthermore, the Examiner also commented that even though Todd teaches a

combination that includes an H_2 antagonist instead of an H_3 antagonist, such as 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, one of ordinary skill in the art would have been motivated to substitute the H_2 antagonist with an H_3 antagonist. For the reasons set forth below, Applicants submit that the Examiner's rejection is respectfully traversed and should be withdrawn.

Contrary to the Examiner's assertions, one of ordinary skill in the art would not have found it obvious to simply substitute H_2 antagonists with H_3 antagonists or inverse agonists as the Examiner has suggested for the treatment of weight gain, much less would one of ordinary skill in the art have made such a substitution based on the teachings of Todd, which is specifically directed toward H_2 antagonists. Todd is in fact purely speculative with regard to weight gain reduction and no experimental results are given. Moreover, effects opposite to those contemplated by Todd were actually reported in the literature following controlled double-blind clinical studies that showed that various H_2 antagonists (such as famotidine and nizatidine) in combination with olanzapine did not decrease the weight gain induced by olanzapine. *See, e.g.*, the attached article by Poyurovsky et al., Eur Neuropsychopharmacol 14(4), 332 (2004) (reporting the absence of weight gain reduction with famotidine); *see also* the attached article by Assuncao et al. 28(4), 270 (2006) (reporting the absence of weight gain reduction with nizatidine).

Furthermore, as set forth in the Declaration of Jean-Charles Schwartz submitted herewith pursuant to 37 C.F.R. §1.132, and as would also be recognized by those of ordinary skill in the art, H_2 antagonists and H_3 antagonists are completely distinct from one another and one of ordinary skill in the art would not have found it a simple matter to

substitute H_2 antagonists with H_3 antagonists for at least the following reasons (which are also discussed in the review by Schwartz et al Physiol Rev 71, 1-51 (1991) attached hereto):

a. H_2 and H_3 receptors are structurally distinct and their genomic structures share poor homology;

b. H_2 and H_3 receptors are present at distinct locations with H_3 receptors being exclusively located in the brain and H_2 receptors being essentially located out of the brain.

c. H_3 receptors are pre-synaptic whereas H_2 receptors are post-synaptic;

d. H_3 receptor antagonism leads to histamine release in the brain whereas H_2 receptor antagonism interferes with histamine actions;

e. H_3 receptors are associated with Gi proteins whereas H_2 receptors are associated with Gs proteins, Gi and Gs proteins having essentially opposite effects;

f. H_3 receptors inhibit the formation of cyclic AMP, whereas H_2 receptors activate the cyclic AMP formation; and

g. H_3 receptors are an electrophysiologically neuronal inhibitor whereas H_2 receptors are is a neuronal exciter.

In light of these differences in H_2 antagonists and H_3 antagonists, it is thus apparent that H_2 antagonists and H_3 antagonists have completely distinct modes of action and have the opposite effects on histamine. Indeed, H_2 antagonists are known to prevent the action of histamine and, in particular, are known to block the action of histamine in the stomach of individuals to thereby decrease gastric acid secretion. In contrast, H_3

antagonists reinforce the action of histamine by causing its release from cells and do so mostly in the brains of individuals, where H_3 receptors are primarily found. As such, and upon a review of Todd, it is thus necessarily that case that one of ordinary skill in the art would not have even contemplated that H_3 antagonists could be combined with an antipsychotic agent to achieve a desired reduction in weight gain. Instead, one of ordinary skill in the art would have used an H_2 antagonist to combat the weight gain caused by antipsychotic agents because Todd clearly and unambiguously teaches away from the inclusion of H_3 antagonists in an olanzapine-containing pharmaceutical composition by indicating that an H_2 antagonist, which has a different mode of action, should be used.

In the Office Action, the Examiner further asserted that it would have obvious to formulate a composition comprised of olanzapine and 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether because Schwartz teaches that 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether is effective in treating obesity and cognitive deficits, and because Schwartz also teaches that H_3 receptor antagonists may be used with psychiatric agents, such as neuroleptics, to increase the efficacy of those agents and to reduce their side effects. However, as pointed out in response to the previous Office Action in this case, Schwartz does not include any teaching or suggestion with respect to the particular side effects that may be countered by administering an H_3 antagonist in combination with an psychiatric agent, and certainly does not teach or suggest which of the side effects of olanzapine can reduced by combining olanzapine with 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether. Indeed, given the fact that obesity is a multi-factorial disease,

Schwartz's mere reference to the use of H_3 antagonists in treating obesity simply cannot be regarded as a teaching or suggestion that 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether could be combined with olanzapine and used to provide a pro-satiety effect and reduce olanzapine's undesirable side effect of weight gain. Accordingly, it is thus the case that neither Schwartz nor Todd include any teaching or suggestion with regard to a specific pharmaceutical composition that includes the olanzapine, as a specific antipsychotic or antidepressant agent, and 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether, as an antagonist or inverse agonist of the histamine H_3 receptor, much less any teaching or suggestions that such a combination could be used to reduce the undesirable side effects associated with olanzapine.

Furthermore, it is also the case that neither Todd nor Schwartz include any teaching or suggestion with regard to the unexpected, synergistic results that were achieved by combining olanzapine with 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether. As described in the attached Declaration of Jean-Charles Schwartz, and as set forth in Example 5 of the present application, Applicants unexpectedly discovered that when olanzapine and 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether (BF2.649) were combined in a pharmaceutical composition, the composition provided synergistic effects that were not observed when either agent was administered individually. In particular, it was observed that when a group of volunteers was administered either a placebo, olanzapine alone (5 mg), BF2.649 alone (60 mg), or a combination of olanzapine (5 mg) and BF2.649 (60 mg) and were then evaluated on their levels of alertness, cognition, and satiety, it was found that olanzapine caused a decrease in alertness and cognition as well

as a marked increase in feelings of hunger. BF2.649 was found to have the opposite effect on those symptoms; however, when a combination of olanzapine and BF2.649 were administered, it was surprisingly found that the combination provided a synergistic effect beyond what was observed when BF2.649 was administered alone. In particular, it was observed that when olanzapine was combined with BF2.649 in the amounts indicated above, a total prevention of the effects of olanzapine on alertness, cognition, and satiety was observed. Such synergistic results are neither taught nor remotely suggested by the cited Todd and Schwartz references.

Similarly, and as shown in the results included in Appendix 1 of the attached declaration of Jean Charles Schwartz, the synergistic effects of combining olanzapine and BF2.649 were also apparent when the effects of that particular combination on feelings of hunger were analyzed and compared to the administration of a control and each separate ingredient alone. From those results, it was apparent that olanzapine greatly induced the hunger of feeling. However, it was further apparent that, when BF2.649 was co-administered, the induced feeling of hunger was totally inhibited and restored to control levels. That total inhibition of side effects induced by olanzapine thus further reflects the synergy exerted by the claimed combination, which again could not have been reasonably expected by the skilled person.

Finally, and in accordance with the new guidelines regarding "Developments in the Obviousness Inquiry after KSR v. Teleflex", 75 Fed. Reg. 53, 643 (effective September 1, 2010), it is also noted that the obvious to try rationale invoked by the Examiner in the present Office Action simply cannot be applied in this case. As set forth

above, one of ordinary skill in the art would not have 1) any reason to substitute an H_2 antagonist with an H_3 antagonist, or 2) a reasonable expectation of success in view of Schwartz or Todd, alone or in combination. Although the Examiner has alleged that, in view of Schwartz, one of ordinary skill in the art would have substituted the H_2 antagonist of Todd with an H_3 antagonist, such an allegation is based on the assumption that H_2 antagonists and H_3 antagonists would even be substitutable with one another in the first place. However, it is noted that Todd only mentions the activity of H_2 antagonists without substantiating it with any experimental results, and thus, one or ordinary skill in the art would not have seriously contemplated the alleged speculative activity, much less have extended the alleged teaching to H_3 antagonists and done so with a reasonable expectation of success.

In summary, it is simply not the case that it would be obvious to one of ordinary skill in the art to simply replace an H_2 antagonist in a composition containing both an H_2 antagonist and olanzapine with an H_3 antagonist, much less would it be expected that such a substituted composition would achieve a desired reduction in the side effect of satiety caused by the olanzapine that is similar to what was purported to be achieved by combining an H_2 antagonist with olanzapine. To the contrary, as discussed above, the distinct effects of H_2 antagonists and H_3 antagonists are well known in the art, and it would not be expected that an H_2 antagonist could be substituted with an H_3 antagonist in a composition containing olanzapine and then used to provide the synergistic results discussed above.

Accordingly, in light of the foregoing discussion, Applicants submit that the present invention is not rendered obvious by the cited references and that the claims of the present application are clearly patentable over those references. Applicants thus submit that the Examiner's rejections on the basis of those references is respectfully traversed and should be withdrawn.

In light of the amendments and arguments provided herewith, Applicants submit that the present application overcomes all prior rejections and objections and has been placed in condition for immediate allowance. Such action is respectfully requested.

Respectfully submitted,

Date: January 12, 2011

By: B. Aaron Schulman
Registration No.: 31,877

STITES & HARBISON PLLC•1199 North Fairfax St•Suite 900•Alexandria, VA 22314
TEL: 703-739-4900 • FAX: 703-739-9577 • CUSTOMER NO. 000881

IN THE U.S. PATENT AND TRADEMARK OFFICE

U.S. Appl. No.:	10/562,396 Confirmation No.: 8440
Title:	COMBINATION PRODUCT COMPRISING AN ANTAGONIST OR INVERSE AGONIST OF HISTAMINE RECEPTOR H_3 AND AN ANTIPSYCHOTIC AND ANTIDEPRESSANT AGENT, AND USE THEREOF FOR THE PREPARATION OF A MEDICAMENT THAT PREVENTS THE ADVERSE EFFECTS OF PSYCHOTROPIC DRUGS
Inventor(s):	Jean-Charles Schwartz, et al.
Filed:	April 14, 2006
Art Unit:	1627
Examiner:	Pihonak, Sarah
Docket No.:	P08824US00/BAS
Customer No.:	000881

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JEAN-CHARLES SCHWARTZ PURSUANT TO 37 C.F.R. §1.132

Sir:

I, Jean-Charles Schwartz declare and state as follows:

1. I am a French citizen and I am an honorary Professor and Chairman at Université René Descartes in Paris, an honorary member of the Institut Universitaire de France, a member of the European Academy (Academia Europea), a member of the French Academy of Sciences. I have also authored over 700 publications in international journals.

2. I am a co-inventor and am familiar with the subject matter described and claimed in the above-identified patent application. The present patent application is directed to a pharmaceutical composition that includes a combination of olanzapine, as an antipsychotic or antidepressant agent, and 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether ("BF 2.649"), as an antagonist and/or inverse agonist B of the histamine H_3 receptor. The composition is capable of suppressing or limiting the increased weight gain, decreased alertness, and decreased cognitive effects that are normally observed during treatment with olanzapine.

3. I have also reviewed the Office Action that was mailed April 12, 2010 and the references cited therein. My understanding is that in conjunction with this application, the Examiner has made the assertion that it would be obvious to one of ordinary skill in the art to simply replace an H_2 antagonist, in a composition containing both an H_2 antagonist and olanzapine, with an H_3 antagonist, and that it would be expected that such a substituted composition would achieve a desired reduction in the side effect of weight gain caused by the olanzapine that is similar to what was purported to be achieved by combining an H_2 antagonist and olanzapine. For reasons as stated below, such is not the case.

4. As an initial matter, the skilled person would have not seriously conceived in view of Todd et al. (WO 00/74784) that H_2 antagonists in combination with olanzapine would decrease weight gain caused by olanzapine. First, Todd et al is in fact purely speculative with regard to weight gain reduction and no experimental result is given. Second, opposite effects were reported in the literature following controlled double-blind clinical studies that showed that various H_2 antagonists (such as famotidine and nizatidine) in combination with olanzapine did not decrease the weight gain induced by olanzapine. For example, see in this respect the attached Poyurovsky et al Eur Neuropsychopharmacol 14(4), 332 (2004 reporting the absence of weight gain reduction with famotidine, and Assuncao et al 28(4), 270 (2006) reporting the absence of weight gain reduction with nizatidine.

5. Moreover, the skilled person considering the teaching of Todd et al, would understand it is not a simple matter to substitute an H_2 antagonist with an H_3 antagonist and/or inverse agonist for at least the following reasons:

a. H_2 and H_3 receptors are structurally distinct: their genomic structures share poor homology;

b. H_2 and H_3 receptors locations are distinct: H_3 receptors are exclusively located in the brain whereas H_2 receptors are essentially located out of the brain. Further, H_3 receptors are pre-synaptic whereas H_2 receptors are post-synaptic;

c. H_3 receptor antagonism leads to histamine release in the brain whereas H_2 receptors antagonism interferes with histamine actions;

d. H_3 receptor is associated with Gi proteins whereas H_2 receptor is associated with Gs proteins, Gi and Gs proteins having essentially opposite effects;

e. H_3 receptor inhibits the formation of cyclic AMP, whereas H_2 receptor activates the cyclic AMP formation; and

f. H_3 receptor is an electrophysiologically neuronal inhibitor whereas H_2 receptor is a neuronal exciter.

These features are reported in the review Schwartz et al Physiol Rev 71, 1-51 (1991), attached hereto.

6. It therefore appears from the above that H_2 receptors antagonists and H_3 antagonists have completely distinct modes of action and have the opposite effects on histamine. H_2 antagonists are known in the art as agents that inhibit the action of histamine and, in particular, are known to block the action of histamine in the stomach of individuals to thereby decrease gastric acid secretion. In contrast, H_3 antagonists reinforce the action of histamine by causing its release from cells, and do so mostly in the brains of individuals, where H_3 receptors are primarily found. As such, one of ordinary skill in the art, knowing this distinction between H_2 antagonists and H_3 antagonists, would not have reasonably considered that a purported effect of combining H_2 antagonists with olanzapine to prevent weight gain could also be obtained with a combination of H_3 antagonists and olanzapine.

7. In addition, it was unexpectedly discovered that when olanzapine and BF2.649 were combined in a composition, the composition provided synergistic effects that were not observed when either agent was administered individually. In particular, when a group of volunteers was administered either a placebo, olanzapine (5 mg) alone, BF2.649 (60 mg) alone, or a combination of olanzapine (5 mg) and BF2.649 (60 mg) and were evaluated on their levels of alertness, cognition, and satiety, it was observed that olanzapine caused a marked decrease in alertness and cognition, as well as a marked increase in feelings of hunger. BF2.649 was found to have the opposite effect on these various symptoms.

8. However, when a combination of olanzapine and BF2.649 were administered in the amounts indicated above, it was surprisingly found that the combination provided a <u>total</u> prevention of the side-effects of olanzapine on alertness, cognition, and satiety.

9. More particularly, results attached herewith as Appendix 1 show the effect on the hunger feeling for the particular combination of BF2.649 with olanzapine compared with control and each separate ingredient administered alone. It appears that:

- olanzapine greatly induces the hunger of feeling; and

- when BF2.649 is administered this induced feeling of hunger is <u>totally</u> inhibited and restored to control levels.

This total inhibition of side effects induced by olanzapine reflects the synergy exerted by the combination. This synergy could not have been reasonably expected by the skilled person.

10. Accordingly, as indicated above, the references cited by the Examiner are also distinguishable from the present claims. For example, Todd et al. (WO 00/74784) is in fact purely speculative with regard to weight gain reduction, and does not provide any data supporting this mere allegation. Further, Todd et al. is specifically directed to H_2 antagonists. H_2 antagonists and H_3 antagonists have completely distinct modes of action. More specifically, H_2 antagonists and H_3 antagonists have opposite effects on histamine: H_2 antagonists prevent the action of histamine, whereas H_3 antagonists reinforce the histamine action. More particularly, H_3 antagonists release histamine in brain: this specific property leads to the prevention of anti-satiety effect of antipsychotic. This histamine release capacity is not shared at all by the H_2 antagonists. The skilled person, knowing this distinction between H_2 antagonists and H_3 antagonists would not have reasonably considered that the speculative effect of combining H_2 antagonists with an antipsychotic to prevent weight gain would possibly have been obtained with a combination of H_3 antagonists and said antipsychotic. This is in fact the opposite that could have been expected: in view of the opposite effect on histamine, the skilled person would have reasonably considered that the effect suggested in Todd et al. would not have been obtained with H_3 antagonist.

11. In addition, the Schwartz reference is cited by the Examiner with regard to the treatment of obesity. However, given the fact that obesity is a multi-factorial disease, mere reference to the use of H_3 antagonists in treating obesity simply cannot be regarded as a teaching or suggestion that 3-(4-chlorophenyl)propyl-3-piperidinopropyl ether could be combined with olanzapine and used to provide a pro-satiety effect.

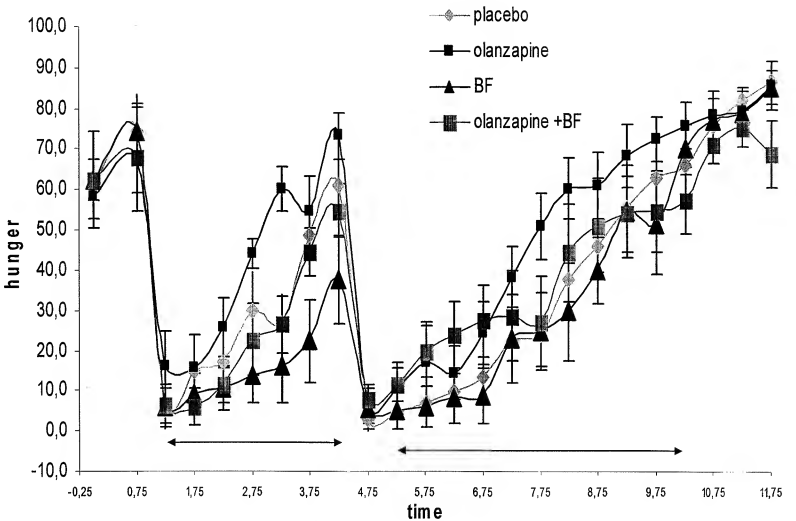
12. Accordingly, the Examiner's assertion that it would be obvious to one of ordinary skill in the art to simply replace an H_2 antagonist in a composition containing both an H_2 antagonist and olanzapine with an H_3 antagonist, and that it would be expected that such a substituted composition would achieve a desired reduction in the side effect on satiety caused by the olanzapine that is similar to what was purported to be achieved by combining an H_2 antagonist with olanzapine, is simply not true. To the contrary, as discussed above, the distinct effects of H_2 antagonists and H_3 antagonists are well known in the art, and it would not be expected that an H_2 antagonist could be substituted with an H_3 antagonist in a composition containing olanzapine and then used to provide the synergistic results discussed above.

I hereby state that all statements made herein based on my own personal knowledge are true and correct and that all statements based on my information and belief are true and correct to the best of my knowledge, and further that all of these statements have been made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18

of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Oct 2020
Date

Jean-Charles Schwartz


placebo
olanzapine
BF
olanzapine +BF
hunger
time
100,0
90,0
80,0
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
-10,0
-0,25
0,75
1,75
2,75
3,75
4,75
5,75
6,75
7,75
8,75
9,75
10,75
11,75

APPENDIX 1

Physiological Reviews

Published and Copyright by
The American Physiological Society

Vol. 71, No. 1, January 1991

Histaminergic Transmission in the Mammalian Brain

JEAN-CHARLES SCHWARTZ, JEAN-MICHEL ARRANG, MONIQUE GARBARG, HÉLÈNE POLLARD, AND MARTIAL RUAT

Unité de Neurobiologie et Pharmacologie, Unité 109, Institut National de la Santé et de la Recherche Médicale, Centre Paul Broca, Paris, France

I. INTRODUCTION

The recognition of histamine (HA) [or 2-(4-imidazolyl)ethylamine] as a messenger molecule in cell-to-cell communication began early in this century. The early history of HA was dominated by Sir Henry Dale, the great British pharmacologist; Barger and Dale (44) were the first to identify the amine in ergot extracts. Thereafter Dale and Laidlaw (151, 152) described the major actions of HA on tissues, i.e., its potent contractile effects on smooth muscles and the capillary dilative action. Popielski (579) described the only other important HA effect, the stimulant effect on gastric secretion.

In 1927, Dale and co-workers (68) were among the first to isolate HA from a variety of fresh tissues, thus establishing that HA is a normal constituent of the body. In fact its name derives from "histos," the Greek word for tissue. However, Dale was reluctant to accept the notion that endogenous HA could function as a messenger molecule, that is, that HA could be released from its tissue stores to affect the activity of target cells. It was Feldberg (211, 212) who clearly demonstrated that HA was released from the lung during the anaphylactic response and that it induced a marked bronchoconstriction.

These experiments suggested the role of HA in the mast cells of connective tissue, which are only one of its major stores. Although HA has long been suspected of not being restricted to mast cells, there was little knowledge of the localization and functions of the non-mast cells stores of the amine until recently.

Insights on possible HA functions in the central nervous system (CNS) have been much slower in arriving than studies on other amines. Nevertheless, the presence of HA in brain can be traced back as far as other biogenic amines (1). Kwiatkovski (426) found that HA was more concentrated in gray matter than in white matter, and White (817) first showed that local synthesis of the amine occurs in the brain.

It was not until 1970 that interest in brain HA resumed when sensitive radioisotopic assays for the amine and for L-histidine decarboxylase (HDC), its synthetizing enzyme, were developed (667, 743). These assays enabled the rapid accumulation of data, mainly biochemical, that indicated that HA needed to be added to the already long list of neurotransmitters. In particular, lesion studies performed by Garbarg et al. (232) demonstrated for the first time the existence of histaminergic neurons in mammalian brain. This was confirmed when immunohistochemical tools to detect the amine (552, 707, 821) or its synthetizing enzyme (802) became available, and the origin and projections of these neurons are fairly well established now. Meanwhile it had been established that cerebral HA could be released by depolarization and in a calcium-dependent manner (32) and that its turnover is rapid and can be modified almost instantaneously (568, 569).

Equally important in establishing the role of HA as a neurotransmitter was the demonstration of the presence in brain of three subclasses of receptors by biochemical (25, 56, 618) and electrophysiological approaches (281).

Thus the two last decades of research have resulted in a coherent picture of the involvement of HA in neuronal communication. In addition, the design of an increasing number of pharmacological tools to selectively modify HA transmission and their utilization in electrophysiological, neurochemical, behavioral, and neuroendocrinological studies has led to a progressively more precise hypothesis about the functions of HA neurons in the CNS.

The topic of HA in mammalian brain has been the subject of various general reviews in the last few years (228, 277, 328, 577, 584, 615, 666). Specific HA neurons and their targets have also been identified in the CNS of the invertebrate mollusk *Aplysia*, but this topic is not considered here (for review see Ref. 811). The topics of brain HA receptors (105, 137a, 227, 255, 256, 304, 334, 659) and of methodology in brain HA research have also been reviewed (238, 786, 805).

II. METABOLISM OF HISTAMINE

A. Biosynthesis

Histamine poorly penetrates the brain from blood (648, 671) and therefore must be formed locally. Indeed, in vivo formation of radioactive histamine in brain was detected after administration of its radioactive precursor L-histidine (His) in cats (818), rats (571), or mice (789). Histamine biosynthesis involves two steps, i.e., transport of His into the cell and its decarboxylation by HDC (for reviews see Refs. 33, 238, 576, 805).

1. Histidine transport

Saturable, energy-dependent His uptake occurs in brain slices (788) and synaptosomes (127, 299, 365). The transport system in synaptosomes seems partly independent of Na^+ and K^+, and kinetic analyses revealed the presence of both high- and low-affinity components. L-Histidine uptake is stimulated by depolarization (299, 788). There is not yet evidence for the presence of a specific His transport system in HA neurons, since amino acid transport is not altered after lesions of the latter (299). However, detection of such a system might be difficult in view of the small number of HA nerve endings in brain. The His level is similar in the C_2 histaminergic and nonhistaminergic neurons of *Aplysia* (813).

2. Properties of L-histidine decarboxylase

L-Histidine decarboxylase (EC 4.1.1.22) and not dopa decarboxylase (EC 4.1.1.28) is responsible for the one-step HA formation in brain (42, 650, 651, 667, 745, 813). L-Histidine decarboxylase has been exclusively purified from various peripheral tissues displaying high

catalytic activity (268, 292, 454, 575, 576, 642, 643, 731, 758, 801, 806, 832) and from most studies appears as a protein of 110-125 kDa constituted of two identical subunits of 55–60 kDa with an isoelectric point around 5.5. The existence of various HDC isoenzymes has been suggested from isoelectric focusing patterns (454, 642, 643) and immunologic studies (804, 805). In addition, variation in the structure of kidney HDC in mouse strains affecting its affinity for its cofactor and its heat stability was shown and attributed to the existence of alleles of a single structural gene on chromosome 2 (455).

However, HDC from various rat tissues, including the brain, displays similar catalytic activity and is similarly recognized by both monoclonal (573–575) and polyclonal antibodies (731). Also HDCs in brain homogenates from *Aplysia californica* (313), rat (667), mouse (745), guinea pig (650, 651), rabbit (516), hamster (296), and human (42) display rather similar catalytic activity. Similar to other mammalian decarboxylases, HDC functions with the cofactor pyridoxal-5'-phosphate, which is so highly bound to the apoenzyme (456, 540, 541) that its addition to cerebral extracts does not result in marked increases in catalytic activity (Schwartz, Garbarg, and Pollard, unpublished observations). Characteristically, HDC decarboxylates His with a Michaelis constant (K_m) and a maximum rate (V_{max}) that change with the pH and ionic strength of the medium (33, 290, 667, 805). At a pH of ~7.0 in standard buffers the K_m of His is ~0.1 mM, a value that appears to be close to the plasma concentration and, presumably, the intraneuronal concentration of the amino acid, accounting for the observations that HA levels in rodent brain are increased after systemic administration of His in large dosages (668, 745). The turnover number of purified HDC (~0.4 s^{-1}) seems low compared with that of other amino acid decarboxylases (454).

Recently, the complete amino acid sequence of rat HDC was deduced from the cloning, from a fetal liver library, of a cDNA encoding the enzyme (367a). It comprises 655 amino acid residues, corresponding to a protein of 73 kDa, a value significantly higher than the 55- to 60-kDa values found after purification of the subunits, suggesting that HDC might be postranslationally processed. Rat HDC displays distinct homologies with other pyridoxal phosphate-dependent enzymes, such as dopa decarboxylase, particularly in the region surrounding the putative cofactor-binding lysine residue (Lys^{397}). The sequence comprises two consensus phosphorylation sites of cAMP-dependent protein kinase. The HDC gene was located to mouse chromosome 2, where it is closely linked to the β_2-microglobulin gene (367a).

L-Histidine decarboxylase displays a high substrate specificity toward His, with the sole other decarboxylated natural amino acid being 3-methylhistidine, which yields *tele*-methylhistamine (*t*-MeHA) (674), a substance with little biological activity that is mainly formed in brain by methylation of HA. Because both the affinity of 3-methylhistidine for HDC and its tissue levels are low, the functional significance of this minor pathway remains doubtful. Other natural amino acids display even lower apparent affinities for HDC, and their decarboxylation was not demonstrated (633). The two HDC inhibitors α-methylhistidine (194, 650) and α-fluoromethylhistidine (412) are decarboxylated by HDC.

In several peripheral tissues, such as the stomach or skin, HDC activity can be rapidly and markedly increased as a result of various treatments, e.g., by hormones (647), that may induce synthesis of HDC molecules (673). In brain, similar changes were not reported but, after its nearly total inactivation by a "suicide-inhibitor," cerebral HDC is synthesized at a high rate: ~50% of the initial HDC activity is recovered within 26 h in the hypothalamus, where HA perikarya are located, and within 58 h in the cerebral cortex, which contains nerve endings (235). From this time lag it has been inferred that HDC is transported at a rate of ~1 mm/h, roughly corresponding to the mean transport rate of other monoamine-synthesizing enzymes.

3. Localization of L-histidine decarboxylase

Biochemical and immunohistochemical studies have revealed the presence of HDC in the cytoplasm of a population of cerebral neurons (see sect. III). L-Histidine decarboxylase activity is distributed in a markedly heterogeneous fashion between cerebral regions, with the highest levels being found in hypothalamus, the lowest levels in cerebellum, and intermediate levels in telencephalic areas (55, 664, 667, 745). Heterogeneous distributions are also found among nuclei of the hypothalamus (567), upper brain stem (572), amygdaloid complex (60), or areas of the hippocampal formation (40). In contrast, HDC activity does not vary markedly between areas of the cerebral cortex (42, 231). These regional distributions of HDC activity are generally consistent with data derived from immunohistochemical studies (see sect. III).

Subcellular fractionation studies indicate that HDC is mainly found in the cytoplasm of isolated nerve endings (55, 745, 751), a conclusion confirmed by immunohistochemical studies at the electron-microscopic level (294). In the hypothalamus, which contains HA perikarya, a lesser proportion of HDC activity than in other areas is associated with subcellular fractions enriched in nerve endings (55), and HDC immunoreactivity is detected all over the cytoplasm surrounding the large cell nucleus of these neurons (294). In the neonatal brain, i.e., before formation of most HA synapses, HDC activity is low, particularly in telencephalic areas, and mainly recovered in soluble (nonsynaptosomal) subcellular fractions (457, 751). The earliest detection of HDC in hypothalamus during postnatal development is consistent with the expression of the enzyme in perikarya from this region (457).

Although HA neurons constitute the major localization of HDC, small fractions of the cerebral enzyme are held in mast cells (457).

4. Inhibition of L-histidine decarboxylase

Because HA is synthesized in a single step and by a highly specific enzyme, HDC inhibitors are potentially

useful tools with which to investigate the role of HA. Until recently, only compounds with limited specificity and low potency, such as α-hydrazinohistidine, brocresine, or α-methylhistidine, were available (433, 667, 668, 743, 745). In 1978, Kollonitsch et al. (412) designed *S*-α-fluoromethylhistidine (α-FMH) among a series of potential "suicide" or catalytic constant (K_{cat}) inhibitors of amino acid decarboxylases. *S*-α-fluoromethylhistidine potently inhibits in a stereoselective, time-dependent, concentration-dependent, and irreversible manner cerebral HDC with an inhibitor constant (K_i) of $\sim 10^{-5}$ M, whereas related decarboxylases such as dopa or glutamate decarboxylase are not significantly affected (235). Indeed α-FMH is a suicide substrate that remains bound to the enzyme after being decarboxylated (194, 421). *S*-α-fluoromethylhistidine is similarly potent on HDCs of humans (763), *Aplysia* (812), and even *Morganella morganii* (295).

From this mechanism it seemed feasible to covalently label and detect HDC autoradiographically on tissue sections; however, because of a high background, this procedure could not be applied to histochemistry (665). *S*-α-fluoromethylhistidine, administered systematically in rather low dosages, rapidly, completely, and in a long-lasting manner inactivates HDC in brain and peripheral organs (82, 83, 235, 296, 446, 692, 792). Restoration of activity occurs progressively, presumably as a result of neosynthesis of HDC molecules, and in brain the process is first detected in the hypothalamus in which HA perikarya are located (235). Because α-FMH efficiently depletes HA stores in cerebral neurons (235, 446), the drug is a useful tool for investigating the amine turnover and functions therein.

5. *Regulation of histamine biosynthesis*

Various treatments that drastically affect HA turnover in brain fail to alter its steady-state level to any large extent, implying the existence of efficient regulatory processes (356, 357, 360, 504, 571). The latter can even be demonstrated to occur in vitro, since the depolarization-induced release of [^{3}H]HA from slices or synaptosomes incubated in the presence of [^{3}H]His is accompanied by a large increase in the rate of [^{3}H]HA formation (23, 26, 28, 787, 788). In the absence of Ca^{2+} in the external medium, not only release but also stimulation of synthesis is abolished, suggesting some relationships between the two effects. However, this interpretation is not entirely clear, since [^{3}H]HA synthesis is already activated by removal of external Ca^{2+} in the absence of depolarization (28).

The mechanism by which external Ca^{2+} regulates [^{3}H]HA synthesis is not known, but parallel changes in catecholamine formation have been ascribed to activation of the rate-limiting enzyme tyrosine hydroxylase by phosphorylation via adenosine 3′,5′-cyclic monophosphate (cAMP)- or Ca^{2+}-dependent protein kinases (252). A similar process was preliminarily suggested to occur in the case of cerebral HDC, the activity of which was enhanced by preincubation with a cAMP-dependent protein kinase (191), but this could not be confirmed on mastocytoma HDC (291). Theoretically, depolarization-induced stimulation of [^{3}H]HA formation could result from an enhancement of [^{3}H]His uptake, but the latter is only weakly enhanced in slices (788) and even decreased in synaptosomes (127, 299). However, stimulation of a quantitatively minor but specific system for the amino acid uptake in HA neurons having so far escaped detection cannot be discarded. A direct feedback inhibition of soluble HDC by added HA has been excluded (668).

Histamine formation in brain slices and synaptosomes as well as in rat brain in vivo is, similar to [^{3}H]HA release, regulated via H_3 autoreceptors (23, 26, 28, 239). In vitro, K^+-induced stimulation of [^{3}H]HA formation is reduced by 60-70% in the presence of HA or H_3-receptor agonists in low concentrations; conversely, it is enhanced by H_3-receptor antagonists, presumably via blockade of autoinhibition elicited by released HA, acting at the autoreceptors. The mechanism of H_3 receptor-mediated regulation of [^{3}H]HA formation is not known, mainly because the transduction system of H_3 receptors is not yet identified.

Stimulation of presynaptic M_1 muscarinic (270) or α_2-adrenergic receptors (271) in slices or in rat brain in vivo also reduces [^{3}H]HA formation to the same extent as H_3 receptor stimulation does.

B. *Storage*

Histamine is present in the brain of invertebrates (607), lower vertebrates (10), and mammals. In several mammalian species, such as dogs (4), cats (5), rabbits (2, 254), monkeys (513, 741), guinea pigs (79), rats (619, 743), mice (629, 660), hamsters (296), and humans (440), it is distributed in a highly nonuniform manner between grossly dissected regions and even among nuclei in regions such as the hypothalamus (98, 567).

A variety of biochemical and pharmacological approaches strongly indicated that the cerebral amine was held in at least two classes of cellular stores, neurons and mast cells (654). With the advent of histochemical methods, these two classes of HA-storing cells have now been visualized (see sects. III and IV). Although mast cells are scarce in the brain, because of their high HA content they significantly contribute to the overall amine content, particularly in certain brain regions.

Data from subcellular fractionation studies (113, 231, 383, 423, 457, 467, 654, 697) are consistent with this dual localization. In mast cells from various tissues, HA is held in large granules that sediment with the crude nuclear (P_1) fraction. Consistently a fraction of cerebral HA (~20%) sediments with this fraction, a feature that is not observed for other amines. In addition, a larger fraction of the amine sediments with both the crude mitochondrial (P_2) and microsomal (P_3) fractions that both contain synaptosomes, i.e., pinched-off nerve endings. Within the P_2 and P_3 fractions, HA is largely bound to vesicles, whereas HDC is mainly soluble: this indicates that HA, similar to other neurotransmitters, is synthesized in the cytoplasm of nerve endings and

thereafter bound to synaptic vesicles. In the bovine retina, ~80% of HA sediments with the heavy P_1 fraction, which contains vascular elements and large nerve endings (513).

Microvessels isolated from homogenates of bovine (362), rat (382), or guinea pig brain (616) have high levels of HA with low HDC activity. In these fractions HA might be held either in endothelial cells or mast cells that are intimately associated with the cerebral vasculature.

C. Release

1. Release in vitro

Endogenous HA is released by K^+-induced depolarization of cerebral slices via a Ca^{2+}- and temperature-dependent process (32, 360, 505, 519, 747). However, on this model the spontaneous efflux of HA is relatively high, as some part of the amine might originate from mast cells, and the K^+-induced stimulation is of limited amplitude, resulting in only 50-100% increases in the HA level in medium. The 20 mM K^+-induced release of endogenous HA from slices of mouse hypothalamus is enhanced at low concentrations of glucose, an effect largely prevented by tetrodotoxin (505).

Tritiated HA synthesized from [^{3}H]His in slices from various brain areas is released by depolarizations induced by K^+ (25, 27, 28, 787, 788), electrical stimuli (781–783), or veratridine (25, 27). This occurs over a low spontaneous efflux and results in a 5- to 10-fold increase in [^{3}H]HA in medium. Release of [^{3}H]HA from depolarized slices is completely inhibited in the absence of Ca^{2+} or in the presence of 10 mM Mg^{2+}, suggesting that it results from the opening of voltage-sensitive Ca^{2+} channels (25, 782, 788). Doubling the external Ca^{2+} concentration diminishes the 30 mM K^+-induced release of [^{3}H]HA, presumably via inactivation of Ca^{2+} channels by an excess of intracellular Ca^{2+} (27). Conducted action potentials are presumably involved for a small part in the 30 mM K^+-induced release, because the latter is only weakly reduced in the presence of tetrodotoxin (27). Neosynthesized [^{3}H]HA is also released from depolarized synaptosomes (27) but not from mast cells (788). All these features are consistent with the idea that depolarization of histaminergic nerve endings induces HA secretion via mechanisms similar to those operating for other neurotransmitters.

Superfused brain slices preincubated in the presence of [^{3}H]HA accumulate the amine against a small concentration gradient (tissue-to-medium ratio of 2) and release radioactivity on depolarizations induced electrically or by K^+ or veratridine (74, 475, 476, 512, 715, 716). Although the Ca^{2+} dependency of the process suggests that [^{3}H]HA originates from neurons, its significance remains doubtful. Indeed, histaminergic neurons apparently lack selective reuptake systems for HA, and the extent of [^{3}H]HA uptake in slices from various brain regions does not parallel the relative densities of HA axons. Moreover, from the effects of neurotoxin-induced lesions it appears that a fraction of exogenous [^{3}H]HA enters dopaminergic and 5-hydroxytryptamine (5-HT) neurons (695).

Compound 48/80, a mast cell degranulator, releases endogenous HA (788) and exogenous [^{3}H]HA (716) but not neosynthesized [^{3}H]HA (788) from hypothalamic slices. In contrast, reserpine, a drug interfering with storage processes in aminergic neurons, releases both endogenous HA (747) and neosynthesized [^{3}H]HA (787) from these slices. These differential effects presumably illustrate the multicompartmentation of the amine in the brain and the fact that, in contrast with the neuronal pool, the slowly turning over pool is not readily labeled by [^{3}H]His. Mast cells do not possess voltage-dependent Ca^{2+} channels in their plasma membrane and therefore do not release HA on depolarization (187, 716).

2. Release in vivo

Spontaneous and K^+-induced release of endogenous HA into superfusates of the hypothalamus of anesthetized cats and freely moving rabbits was detected (560, 562). The spontaneous release appeared to vary rhythmically in hypothalamus but also in mammillary bodies or medial amygdaloid nucleus (583). After lesions of the ascending histaminergic pathway at the hypothalamic level, the HA content in the cerebral cortex transiently rises, which may reflect an impaired release resulting from the interruption of impulse flow (40, 231). Electrophysiological responses triggered in the cerebral cortex (640), hippocampus (284, 285), or nucleus accumbens (126) by large stimulations of putative afferent pathways were significantly impaired by iontophoretic application of HA receptor antagonists.

These observations may be taken as indirect evidence for a stimulation-induced release of endogenous HA in vivo.

3. Control of histamine release by autoreceptors and heteroreceptors

In slices from several regions of rat brain the release of neosynthesized [^{3}H]HA induced by either K^+ (25–27), veratridine (25–27), or field electrical stimulation (781–783) is strongly inhibited on addition of exogenous HA in the external medium. In overflow experiments, the maximal inhibition of release may be as high as 80% with 30 mM K^+ stimulations (666) or nearly total with electrical stimulation (782, 783). Inhibition is more marked for depolarizing stimuli of low intensity (27). The autoinhibitory effect of HA appears to be a receptor-mediated effect, since it displays saturability [the half-maximal effective concentration (EC_{50}) of HA is ~0.1 μM], reversibility (it is suppressed by washing out the excess of exogenous HA from the preparation), and high pharmacological specificity, being mimicked or antagonized in a competitive manner by several agents displaying low if any activity at H_1 and H_2 receptors.

This last feature has led to the pharmacological definition of H_3 receptors (23, 25). The fact that H_3 receptors are directly located on histaminergic terminals was shown by various data: *1*) the autoinhibitory effect of HA persists when the propagation of action potentials in the brain slice is blocked by tetrodotoxin, *2*) it also persists in slices from kainate-injected striatum, and *3*) it is also found with a synaptosomal preparation (26, 27). The extent of the autoinhibition can be modulated in a complex manner by changes in extracellular Ca^{2+}, suggesting that H_3 receptors regulate HA release via a control of Ca^{2+} entry (27).

The fact that selective H_3-receptor antagonists modestly but significantly enhance [^{3}H]HA release from depolarized slices and, when systematically administered, markedly enhance cerebral HA turnover indicates that H_3 receptors are tonically activated in vivo (23, 239, 519a). This observation might be related to the fact that endogenous HA concentration in human lumbar cerebrospinal fluid (CSF) ($\sim$0.4 μM) is above the EC_{50} of HA at H_3 receptors (34, 388, 714). However, HA levels were found to be clearly lower when assayed by different methods (776a), and HA levels in ventricular CSF or extracellular fluid of the brain are not known.

Release of neosynthesized [^{3}H]HA from rat brain slices and synaptosomes is inhibited by stimulation of muscarinic M_1 receptors (270), α_2-adrenoreceptors (271, 310, 312), and opioid κ-receptors (271a). In contrast, [D-Ala^2-N-Me-Phe^4,Gly^5-ol]enkephalin (DAGO), a specific agonist at μ-opiate receptors stimulates the 30 mM K^+-evoked HA release from mouse brain slices (360). Hence not only auto- but also heteroreceptors appear to control the amine release.

D. Inactivation

1. Uptake

In several studies with brain slices or synaptosomes, no evidence for an active transport system for HA operating at histaminergic nerve endings could be found (324, 489, 664, 740). In contrast, uptake of labeled HA in brain slices, occurring against a limited concentration gradient, was reported in other studies (74, 475, 476, 512, 716, 778), some of which also demonstrated that the radioactivity could be subsequently released by depolarization (see sect. II*C*). However, the maximum tissue-to-medium ratio was low, the energy dependence of the process not demonstrated, the regional distribution of this accumulation did not reflect that of HA neuronal markers, and finally release of accumulated [^{3}H]HA was not regulated by H_3 autoreceptors. This suggests that no significant uptake occurred at HA nerve endings. On the contrary, recent lesion studies indicate that a fraction of [^{3}H]HA is accumulated into serotoninergic and dopaminergic neurons (695). In summary, HA neurons appear to be almost unique among monoaminergic neurons in that they lack a high-affinity reuptake system.

2. Transmethylation of histamine

In various tissues, HA catabolism occurs along two alternative pathways, i.e., transmethylation into *t*-MeHA catalyzed by histamine *N*-methyltransferase (HMT, EC 2.1.1.8) and oxidative deamination into imidazolacetic acid, catalyzed by diamine oxidase (histaminase, EC 1.4.3.6) (602, 603, 645). Contrary to an early report (698), only the former pathway operates in mammalian brain, as shown by the failure to detect diamine oxidase activity (103) or formation of labeled imidazolacetic acid after intracerebral administration of labeled HA; in contrast, both *t*-MeHA and its deaminated metabolite *tele*-methylimidazole acetic acid (*t*-MIAA) were detected (648, 649, 671). Low levels of *t*-MeHA are present in monkey and human CSF (389, 585, 722, 723).

Methylation also appears to be the main, presumably the only, pathway for the catabolism of endogenously synthesized [^{3}H]HA in vivo (571, 601, 602, 648, 649, 672, 818) or in vitro after its depolarization-induced release (27, 788). Endogenous *t*-MeHA is present in brain at levels in the same range as those of HA and with a similar regional distribution (238a, 330, 336, 521, 522, 629). The large decreases in *t*-MeHA levels elicited by inhibition of either HDC (521, 522, 629) or HMT (339) imply that in vivo *t*-MeHA is mainly formed by HA methylation. However, a small contribution of the pathway involving decarboxylation of the natural amino acid *tele*-methylhistidine by HDC cannot be dismissed (674). Subcellular fractionation indicates that, in contrast to HA, *t*-MeHA is more abundant in the supernatant than in synaptosome-containing fractions (336), suggesting its predominantly extraneuronal formation.

tele-Methylhistamine is inactive at H_1, H_2 (226), and H_3 receptors (25). The activity of HMT is high in the brain of various mammalian species in which its rather homogeneous regional distributions does not reflect that of HA neuron markers (36, 96, 628, 664, 771, 777). On subcellular fractionation, cerebral HMT is mainly recovered in the supernatant, with a rather minor contribution of the soluble fraction from synaptosomes (95, 423). Histamine *N*-methyltransferase is present in both glioma and neuroblastoma cell lines (236) as well as in cerebral microvessels (382). Neither lesion-induced degeneration of HA neurons nor intrahippocampal kainate (234) significantly affect telencephalic HMT (75, 237). In contrast, HMT was reduced in the striatum after local administration of kainate (699) and in the neurohypophysis after section of the pituitary stalk (785). Although HMT has not been visualized histochemically, all these data suggest that HMT is present in the cytoplasm of a variety of cerebral cells into which released HA has to enter (see sect. II*D1*). Diurnal (777) and hypertonic saline-induced (785) variations in neurohypophyseal HMT have been described.

Histamine *N*-methyltransferase from various tissues has been purified to homogeneity (88, 293, 460) and its properties reviewed (81, 736). The enzymes from brain and kidney have similar physicochemical, catalytic, and immunologic properties. They have a M_r of 30,000, a pI of 5.3, and an optimum pH for HA methylation of 7.5–9.0.

They catalyze the transfer of a methyl group from the universal donor *S*-adenosyl-L-methionine selectively to the *tele*-nitrogen of the imidazole ring of HA. The K_ms of both substrates are ~10 μM. No endogenous substrate other than HA has been identified. In vitro, HMT is inhibited by HA at concentrations > 100 μM (47, 460, 746), but this may not have physiological relevance. Histamine *N*-methyltransferase is also inhibited by its two reaction products, i.e., *t*-MeHA (96, 439) and *S*-adenosyl-L-homocysteine (53, 529, 664, 837), with K_is in the same range as the K_ms of its two substrates, implying a possible regulatory role (664). Although a different kinetic mechanism was proposed (748), a variety of features indicate that HMT functions with an ordered bi-bi-mechanism (30, 53, 219, 530).

In vitro, HMT can be inhibited by a large variety of drugs including H_1-, H_2-, and H_3-receptor antagonists (for review see Ref. 786), with one of the most potent compounds being SKF 91488, a dimaprit analogue devoid of activity at receptors (58). In vivo, the most effective compounds to inhibit cerebral HMT are amodiaquin (664, 748) and, even more, metoprine (192). The latter decreases *t*-MeHA (339, 357, 835) and increases HA in rat brain (192, 838), confirming the key role of HMT in HA inactivation.

3. *Oxidative deamination of tele-methylhistamine*

The cerebral levels of radioactive *t*-MeHA formed from either labeled HA (648, 649, 671) or labeled His (571, 601) rise markedly in rodents treated with monoamine oxidase (MAO) inhibitors, such as pargyline, that are devoid of diamine oxidase inhibitory capacity. These drugs also increase endogenous *t*-MeHA (238a, 338, 522). This occurs without marked changes in levels of endogenous or labeled HA. Hence MAO seems responsible for the oxidative deamination of *t*-MeHA. The type B isoenzyme of MAO catalyzes the reaction, as shown with MAO inhibitors more selective than pargyline (329, 796).

Deamination of *t*-MeHA results in the formation of *t*-MIAA (645), which therefore represents the final product of HA metabolism in mammalian brain (339, 648, 649). Its level is reduced, although slowly, after inhibition of either HMT (339) or HDC (721). Probenecid, a drug inhibiting the active transport of deaminated metabolites of various monoamines from brain, does not apparently affect that of *t*-MIAA (387, 671). Endogenous *t*-MIAA is present in monkey and human CSF at levels slightly higher than those of *t*-MeHA (389, 585, 723).

4. *Other inactivation pathways*

The good agreement between turnover rates derived from the application of various methods indicates that formation of *t*-MeHA and its subsequent deamination constitutes the major if not the sole metabolic pathway for cerebral HA (see next section). Although mammalian brain contains an *N*-acetylhistamine deacetylase (205, 297), endogenous acetylation of HA is not substantiated.

In invertebrates a major inactivation pathway for HA may consist of the formation of the peptidoamines γ-glutamyl-HA (703) or α-alanyl-HA, i.e., carcinine (20). Peptidoamines are also formed when HA and various amino acids are incubated with brain homogenates, but the physiological relevance of this observation has remained obscure (413, 599).

E. *Turnover*

Isotopic tracer methods, the first to be applied to the determination of HA turnover rate in brain, revealed that the half-life of the amine is a matter of minutes and can be altered almost instantaneously (170, 571). These early observations, which supported the contention that HA was released from neurons, have been essentially confirmed and extended with the development of various nonisotopic methods (for reviews see Refs. 258, 629).

1. *Isotopic methods*

With no selective uptake mechanism to mix radioactive HA to the endogenous stores, the latter must be labeled with the radioactive precursor to realize turnover studies. In early studies, [^{3}H]His was administered intracerebroventricularly in lightly anesthetized rats, and the fluctuations of the specific radioactivities of [^{3}H]HA and [^{3}H]His were typical for a precursor-product relationship in a single open compartiment (170, 571). Analysis of this relationship using two different mathematical models led to values of 46 min (571) and 30 s (170) for the half-life of HA in whole brain. Neosynthesized [^{3}H]HA was localized in subcellular fractions containing nerve endings (571). However, the mode of administration of the tritiated precursor is unphysiological and results in a nonuniform labeling of various brain areas.

These drawbacks are avoided by intravenous administration of [^{3}H]His either in a pulse or at a constant rate (23, 660, 789). The mean half-life of HA in mouse brain was 46 min after constant rate infusion (660), a value similar to that found in rat brain (571), and 20 min after pulse injection (660). The values did not markedly differ between regions; however, there was a slightly shorter half-life in pons-medulla. The half-life of HA was much shorter in brain than in any peripheral organ (660).

2. *Nonisotopic methods*

Among the various experimental approaches that could theoretically be applied to the evaluation of HA turnover rate, only two have been extensively used; they consist of determining the rates of endogenous HA decline and *t*-MeHA elevation after inhibition of HDC and MAO, respectively.

After irreversible inactivation of HDC by α-FMH, HA levels decrease rapidly in mouse, guinea pig, and rat

brains (23, 235, 447, 507, 629). However, even a few hours after nearly total inactivation of HDC, the amine depletion is not complete, evidencing the presence of a resistant pool with a very slow turnover, the existence of which was already suggested in studies with less potent and reversible inhibitors (744, 745). The mean maximal HA depletion by α-FMH is ~50% but varies among CNS areas and animal species; in all species, no significant depletion occurred in the spinal cord (235, 507, 522, 629). The depletion of HA is rapid in a subcellular fraction containing nerve endings (23), indicating that HA turnover is rapid in neurons, but the cellular localization of the slowly turning over pool is still debated. In the brain of W/W^v mice, a mutant devoid of mast cells, HA levels are lower than in congenic normal mice and, in contrast to the latter, are almost completely depleted by α-FMH (447, 793, 833). However, this difference has not been confirmed in other studies (269, 335, 528).

The mean half-life of HA in the rapidly turning over pool is 30 min in rat, mouse, and guinea pig brains (23, 521, 522, 629). Whereas steady-state levels of HA vary markedly among regions, this is generally not the case for half-lives, but slightly higher values are found in the hypothalamus where HA perikarya are present.

After administration of pargyline, a MAO inhibitor, endogenous *t*-MeHA levels rise (238a, 337, 338, 521, 522, 629) at a rate that is likely to reflect that of HA release (571). From this rise, and with some assumptions, half-lives for HA can be derived that are generally in the same order as those obtained using synthesis inhibition or isotopic methods. Again the HA half-life is the longest in the hypothalamus, and the pargyline-induced rise in *t*-MeHA is negligible in spinal cord.

One potential limitation of these nonisotopic methods is that they require the administration of drugs in high dosages to completely block a metabolic pathway, and this could affect directly or indirectly the activity of histaminergic neurons. However, pargyline treatments, which are likely to affect several monoamines, do not generally modify HA steady-state levels (629) or turnover measured with [^{3}H]His (571).

3. Drug-induced changes in turnover

Histamine turnover in rat brain is reduced almost instantly on administration of barbiturates and a variety of hypnotics or anesthetics (37, 568, 571). Similar effects are observed with other "sedative" agents, such as the γ-aminobutyric acid (GABA)-mimetic drugs muscimol and benzodiazepines (506, 520), ethanol (356), and Δ^9-tetrahydrocannabinnol (519), the latter attributed to an inhibition of HA release. Other agents inhibiting HA release in vitro via stimulation of presynaptic histamine H_3, α_2-adrenergic, or muscarinic M_1 receptors reduce HA turnover in vivo (23, 270, 271). In contrast, reserpine, a drug interfering with the storage mechanisms of monoamines and releasing HA in vitro (747, 787), accelerates HA turnover (569). In vivo, blockade of H_3 receptors (23, 239, 519a) but not muscarinic or adrenergic receptors (270, 271) accelerates HA turnover, suggesting that only H_3 receptors are tonically activated in vivo.

Morphine (504), DAGO, a specific agonist at μ-opiate receptors (360), and [D-Ala^2,D-Leu^5]enkephalin, a nonspecific agonist at δ-opiate receptors, but not ethylketazocine, an agonist at κ-opiate receptors (359), enhance HA turnover. The psychotomimetic agent phencyclidine has a similar effect, which is blocked by naloxone, an opiate receptor antagonist (357, 359). After the various treatments modifying HA turnover, Saeki and co-workers (504, 519, 520) found that the steady-state level of *t*-MeHA was modified in an apparently unrelated manner, suggesting that this level does not constitute a reliable turnover index.

III. DISPOSITION OF HISTAMINERGIC NEURONAL PATHWAYS

In 1974, the decrease of HDC activity found in many rat brain areas after lesions of the lateral hypothalamic area was the first evidence for the existence of an ascending HA neuronal pathway with widespread projections to almost all regions of mammalian brain (232). Ten years later, the exact localization of HA perikarya in the posterior hypothalamus was established immunohistochemically using HA (552, 707) and HDC antibodies (802, 803). During the same period, HA neurons had been identified in *Aplysia* brain by biochemical analysis of microdissected tissues (813).

A. Lesion Studies

The rough disposition of HA pathways in rat brain, initially established by lesion studies, is now confirmed and obviously largely extended by immunohistochemical data. Hence these studies, which are reviewed in detail elsewhere (666), are rapidly summarized here.

Unilateral interruption of the medial forebrain bundle leads to ipsilateral decreases in HDC activity (by 50-55%) and HA levels (by 25-30%) in telencephalic and diencephalic areas rostral to the lesion (231, 232). The existence of ascending fibers emanating from the same bundle was also deduced from the effects of discrete lesions of the afferents to the hippocampal region (40) and amygdaloid nuclei (60). From the analysis of a series of discrete lesions in the mesodiencephalon a localization of corresponding perikarya in the mammillary region of the hypothalamus (and the neighboring mesencephalic reticular formation) was suggested (233). Finally, the existence of a descending HA pathway emanating from the posterior hypothalamus and projecting rather heavily to various brain stem nuclei was proposed (572).

Recently, unilateral lesions with ibotenic acid in the vicinity of the mammillary bodies (where HA perikarya are located) induced bilateral reductions in HA levels in the hypothalamus and frontal cortex but an ipsilateral

reduction in hippocampus. In contrast, HA levels increased markedly in the neurohypophysis (501).

B. Immunohistochemical Tools

The precise localization of HA neurons could be established with the advent of several reliable immunohistochemical tools. High-affinity polyclonal antibodies to a highly purified, although not homogeneous, preparation of HDC obtained from rat fetal liver (731, 803) have found the largest applications in several laboratories. These antibodies cross-react with dopa decarboxylase in guinea pig (but not rat) brain (16, 732) and apparently cannot be used for immunohistochemistry in species other than rats. The antibodies for HDC developed earlier (224, 758) were less specific. Despite its specificity, a monoclonal antibody to partially purified HDC from rat stomach has found only limited histochemical applications because of its rather low affinity (573–575).

Polyclonal antibodies to HA raised against the amine either simply mixed with serum albumin (531, 821) or conjugated to proteins using aldehydes (707, 708) or carbodiimide (550–552) have been also used as histochemical tools. Among these, the latter appear as the most reliable tools, especially when the detection sensitivity is enhanced by using carbodiimide as a tissue fixative (550). In contrast, other HA antibodies were found to detect numerous immunoreactive fibers or neurons in areas, such as the median eminence (707, 821), in which they seem absent or very scarce (351), an artifact presumably related to cross-reactivity with histidine-containing peptides, such as luteinizing hormone-releasing hormone (LHRH) (64).

C. Localization of Histaminergic Perikarya: Tuberomammillary Nucleus

Strikingly consistent results were obtained in various laboratories regarding the localization of histaminergic perikarya, whatever the immunohistochemical tool used, i.e., either the anti-HDC monoclonal (573, 574) or polyclonal antibodies (207, 350, 606, 803, 804, 829) as well as the anti-HA antibodies (550–552, 707, 708). Hence HA perikarya, mostly large cells, were found to be confined to the tuberal region of the posterior hypothalamus in an area where a group of Nissl-stained magnocellular neurons had been detected earlier and collectively named the tuberomammillary nucleus (TM) (165, 474; Fig. 1). Two groups of Nissl-stained magnocellular neurons were also detected later in the same area by Bleier et al. (80), who named them the caudal magnocellular nucleus (CMC) and the tuberal magnocellular nucleus (TMC). The same region is included in an "efficient area" defined by analyzing combined lesion data and proposed to contain HA perikarya projecting to the telencephalon (233). Other previous data are consistent with this localization: the neurotoxin kainate decreases HDC in this area, presumably by ablating HA perikarya, whereas colchicine has an opposite effect, presumably by blocking the enzyme axonal transport (233).

Whereas in previous studies HA perikarya were considered to belong to several distinct nuclei, generally named after Bleier et al. (80), Ericson et al. (207), in the most comprehensive anatomic study of this area performed at the light-microscopic level with the anti-HDC antibodies of Watanabe et al. (803), provided convincing evidence for the HA perikarya making up one continuous cell group. The latter, named the TM after Morgan (474) and a previous study of the same laboratory (411), was divided in several subgroups, generally in agreement with studies of other laboratories, although the nomenclature differs (for a correspondence see Fig. 1).

The medial tuberomammillary subgroup (TMM) is constituted of ~600 neurons situated on each side of the mammillary recess. It can itself be subdivided into *1*) a dorsal part (TMMd) corresponding to the TMC of Bleier et al. (80), i.e., an isolated group of cells extending over 1.5 mm along the tip of the third ventricule between the dorsal premammillary nucleus and the dorsomedial nucleus; and *2*) a ventral part (TMMv) close to the ventral surface of the brain just rostral to the medial mammillary body, occurring as a cluster of cells located dorsolaterally to the infundibular nucleus and the mammillary recess. This cluster is bridged (207, 827) by isolated immunoreactive cells with the ventral tuberomammillary subgroup (TMV).

The TMV, the largest one comprising ~1,500 mostly magnocellular neurons, is subdivided by the mammillary bodies into *1*) a rostral part (TMVr), corresponding to the CMC of Bleier et al. (80), situated just in front of the lateral mammillary nucleus; and *2*) a caudal part (TMVc), corresponding to the posterior caudal magnocellular nucleus of Bleier et al. (80), situated behind the lateral and medial mammillary bodies and the supramammillary nucleus.

The diffuse part of the tuberomammillary nucleus (TMdiff) is constituted by a small number (~100) of HDC-immunoreactive cells scattered within or between various hypothalamic nuclei in the lateral hypothalamic area, the posterior hypothalamic area, the perifornical area, and the supramammillary and dorsomedial nuclei. Most of them were detected in previous immunohistochemical studies (573, 574, 707, 708, 803, 804), but they were only recently considered (207, 411) as belonging to a single subset.

Histamine perikarya are immunodetectable in rat hypothalamus during late fetal stages (35, 605) and can be cultivated for several days in vitro (550).

Although most anatomic studies were performed in rats, the TM was first identified in Nissl-stained sections of the dog hypothalamus (474) and seems present in all mammals, becoming more differentiated in primates and most extensive in humans (165, 411). With the use of antibodies against HA, perikarya were also localized in the mammillary region of guinea pigs: they seem more numerous than in rats, being also found between the medial and lateral mammillary nuclei as well as between the premammillary nuclei (7). In cat hypothalamus, magnocellular neurons becoming immunoreactive to 5-HT antibodies after treatments with 5-hydroxytryptophan (5-

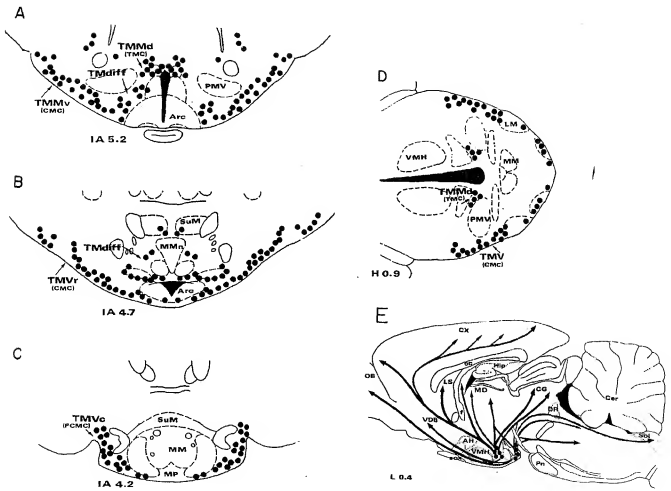


FIG. 1. Localization of histaminergic perikarya (closed circles) in tuberomammillary nucleus and disposition of main histaminergic pathways (arrows) in rat brain. Sections represented according to atlas of Paxinos and Watson (553a). The subgroups of perikarya in tuberomammillary nucleus are designated according to Morgan (474), Diepen (165), and Köhler et al. (411), and corresponding nomenclature according to Bleier et al. (89) is indicated within parentheses. *A*, *B*, and *C*: frontal sections at indicated levels of caudal hypothalamus. *D*: horizontal section through caudal hypothalamus. *E*: sagittal section of brain. Abbreviations of perikarya subgroups: CMC, caudal magnocellular nucleus; PCMC, posterior caudal magnocellular nucleus; TMC, tuberal magnocellular nucleus; TMdiff, tuberomammillary nucleus diffuse part; TMMd, medial tuberomammillary subgroup dorsal part; TMMv, medial tuberomammillary subgroup ventral part; TMV, ventral tuberomammillary subgroup; TMVc, ventral tuberomammillary subgroup caudal part; TMVr, ventral tuberomammillary subgroup rostral part. Other abbreviations: AH, anterior hypothalamic area; Arc, arcuate nucleus; cc, corpus callosum; Cer, cerebellum; CG, central gray; CX, cerebral cortex; DR, dorsal raphe nucleus; f, fornix; Hip, hippocampus; LM, lateral mammillary nucleus; LS, lateral septum; MD, mediodorsal thalamus; MM, medial mammillary nucleus medial part; MMn, medial mammillary nucleus median part; MP, medial mammillary nucleus posterior part; OB, olfactory bulb; PMV, premammillary nucleus ventral part; Pn, pontine nuclei; Sol, nucleus of solitary tract; Sox, supraoptic decussation; SuM, supramammillary nucleus; VDB, nucleus of vertical limb of diagonal band; VMH, ventromedial hypothalamic nucleus.

HTP) seem to correspond to HA neurons and extend from the suprachiasmatic nucleus to the caudal end of the hypothalamus (632, 636, 637). Histamine-immunoreactive perikarya were also detected in the human mammillary region (549, 549a). In all these species the HA magnocellular neurons seem less aggregated than in rats but otherwise display very similar features.

In one study immunoreactive HDC (irHDC) horizontal cells were detected in the guinea pig retina (17), but this could not be confirmed using an anti-HA antibody (7).

D. Morphology of Histaminergic Neurons

The HA neurons of the TM display a series of characteristic features, as revealed in the various immunohistochemical studies at the light-microscopic level (see sect. III*C*) or electron-microscopic level (296, 825, 829).

Most of them are large (25–35 μm) neurons, particularly in the TMV (since the TMM contains a large number of medium-sized cells), with a round unindented nucleus, a well-developed Golgi apparatus, and a relatively large

amount of karyoplasm. Very similar ultrastructural characteristics are found in noradrenergic or serotoninergic perikarya as well as in the cholinergic perikarya of the basal nucleus of Meynert.

Another characteristic feature at TM cells is their dendritic processes comprising two to three thick primary dendrites dividing into long (100-150 μm) secondary dendrites, with few spines and axodendritic synaptic contacts. The dendritic trees of adjacent neurons overlap each other. In one study it was observed that the dendrites narrowed down into varicose fibers filled with small vesicles similar to synaptic vesicles, and it was hypothetized that exocytosis might occur at this level (445), but this was not confirmed in another study in which the varicose fibers emerging from the emission cones of dendrites were identified as axons (825).

Another very characteristic feature is the close interaction of dendrites with glial elements in the mammillary recess and the ventral surface of the brain in a way suggesting that the dendrites penetrate into the ependyma and come into close contact with the CSF. The exact functional significance of this peculiar organization is still obscure, but it has been proposed that HA neurons might either release their secretions into the CSF (445) or respond to CSF-borne substances (606).

Finally, in one ultrastructural study, both myelinated and unmyelinated irHDC varicose axons, making few typical synaptic contacts, were observed in the TMV (294). This was interpreted as evidence for a mainly nonsynaptic release of HA, similar to that proposed for other monoamines (57), but the relationships of these elements with the varicose dendrites of Maeda et al. (445) remains to be clarified.

E. Other Putative Transmitters in Histaminergic Neurons

The HA neurons in TM are characterized by the unusual presence of a large variety of markers for other neurotransmitter systems, some of which evidenced before or independently from the demonstration of HA itself.

Glutamic acid decarboxylase, the GABA-synthesizing enzyme, was first evidenced in TM neurons projecting to the cerebral cortex by Vincent et al. (791), and its colocalization with the vast majority of irHDC neurons (679, 734, 825) was shown soon later.

In a parallel manner, Nagy et al. (478) evidenced in TM neurons the presence of adenosine deaminase, a cytoplasmic enzyme that might be responsible for the inactivation of the putative neurotransmitter adenosine. Presence of this marker in the vast majority of irHDC perikarya was demonstrated soon after (553, 679, 700). Tuberomammillary nucleus neurons also express binding sites for a putative ligand of adenosine uptake sites (477).

A majority of irHDC neurons also stain with antibodies against galanin, a 29-amino acid neuropeptide (410, 466, 700). Interestingly galanin is also colocalized with other amines, i.e., catecholamine, 5-HT, and acetylcholine in other cerebral neurons (466).

Also a majority of TM neurons stain with antibodies raised against the opioid heptapeptide (Met^5)enkephalyl-Arg^6-Phe^7, suggesting that they express the proenkephalin A gene (411, 822).

Staining of at least a fraction of TM neurons with antibodies against two other neuropeptides, i.e., substance P (411) or thyrotropin-releasing hormone (TRH) (688) was also reported.

Another characteristic feature of a rather large subpopulation of TM neurons is the presence of high MAO B activity, possibly related to deamination of *t*-MeHA (392, 393, 444, 445, 700, 730). This subpopulation, representing ~60% of neurons expressing both HDC and adenosine deaminase, could be the same as that expressing enkephalins (730).

Finally, a fraction of TM neurons have the capacity to uptake and decarboxylate 5-HTP into 5-HT (which is then detected immunohistochemically) but not to synthesize 5-HT after tryptophan administration (445, 632, 637, 700). This suggests that some TM neurons express not only HDC, for which 5-HTP is not a substrate, but also the aromatic amino acid decarboxylase (EC 4.1.1.28) and thereby resemble the peripheral APUD cells (554).

The fact that such a high number of neurotransmitter markers are apparently expressed by the same TM neurons raises several comments: *1*) these colocalizations have been established by purely histochemical approaches and require confirmation by other approaches; *2*) the biological significance of some markers, e.g., adenosine deaminase or 5-HTP uptake and decarboxylation activities, is not fully clarified; and *3*) the delineation of neuronal subpopulations within the TM, taking into account which among the eight markers listed above are coexpressed by each cell, has only started (410, 679, 700). Finally, and most importantly, establishing the functional significance of the colocalization of such a high number of messengers in a single population of neurons still remains an important and exciting challenge.

F. Pathways and Projection Fields of Histaminergic Neurons

Although some fibers were detected in the early immunohistochemical studies (552, 573, 574, 707, 708, 731, 805), it is only recently that technical improvements have started to reveal the extensive networks of irHDC (350) and irHA (7, 551) fiber systems in brain that were already suggested by lesions (232). This information has been complemented by that provided by retrograde tracing studies, sometimes performed before the realization that HA perikarya were located in the TM.

Histamine neurons constitute long and highly divergent systems projecting in a diffuse manner to many cerebral areas (232), with immunoreactive varicose or nonvaricose fibers being detected in almost all regions of frog (7a), rat (350, 551), guinea pig (7), tree shrew (6a), or human brain (549, 549a). Despite initial suggestions that

the various TM subgroups might have distinct projection fields (708, 709), more recent retrograde tracing studies have established that TM neurons are not organized in a highly topographic way, since individual neurons give rise to projections to widely divergent parts of the forebrain, cerebellum, and mesencephalon (207, 411).

Panula et al. (551) distinguished two ascending pathways in rat brain. The ventral pathway runs at the basal surface of the brain toward the horizontal limb of the nucleus of the diagonal band and then to the medial septal nucleus or the olfactory tubercle and bulb, with a large fraction of the fibers crossing the midline in the retrochiasmatic area. The dorsal pathway runs along the lateral side of the third ventricle and contributes to fibers ending in thalamus and rostral forebrain structures (Fig. 1).

Moderately dense HA fibers are quite evenly distributed in all areas and layers of the cerebral cortex (7, 350, 551, 707, 708, 735, 803). In human cerebral cortex they appear to be most abundant in the external layers where they run in parallel to the surface (549, 549a). Deafferentation studies have established that they are extrinsic (41, 232, 735), and retrograde tracing studies showed that they emanate from the TM (207, 411, 478, 632, 708, 709, 784, 791), ascending through the medial forebrain bundle itself (232), which contains numerous fibers in rats (350, 551) or in guinea pigs an area between this bundle and the optic tract (7).

From studies combining lesion and biochemical (231–233) or immunohistochemical (735) analysis of HDC, it appears that the cerebral cortex receives predominantly ipsilateral projections of HA fibers. However, a minor participation of a contralateral projection, representing only about one-fifth to one-third of the total, was shown by retrograde tracing (411, 478, 735, 791) and antidromic activation studies (604). Midline crossing of these fibers occurs at the level of the retrochiasmatic area, the optic chiasma, and in the supramammillary region (350, 551) and was overlooked in combined unilateral lesion and biochemical studies (231, 232), presumably because of its limited extent and inherent individual variation among control (nonlesioned) animals. The extent to which crossing of fibers originating from the TM occurs seems to vary according to the innervated brain area, but there is, in most cases, a majority of ipsilateral fibers (207, 411).

In a variety of other telencephalic areas, immunohistochemical studies, sometimes combined with retrograde tracing, have shown long ascending connections between perikarya in the TM and the olfactory bulb (mainly in the external plexiform layer), hippocampus (mainly in dentate gyrus and subiculum), nucleus accumbens, globus pallidus, and amygdala (7, 207, 350, 550, 551, 708, 709, 828). In the caudate-putamen, fibers are surprisingly scarce when detected with anti-HA antibodies (551) but are considerably more numerous when detected with anti-HDC antibodies (350, 803). This general organization of HA pathways is in agreement with previous deafferentation or focal lesion-induced changes in HDC in some of these areas, i.e., the amygdaloid complex in which a very rich HA innervation is present (60) or the hippocampus (40). These studies suggested that, in rats, HA fibers reach the amygdaloid complex via the ansa peduncularis and the hippocampus via a dorsal route comprised of the fimbria, fornix superior, and cingulum; in agreement immunoreactive fibers seem abundant in rat fimbria (350, 551) but very scarce in the guinea pig fimbria and fornix (7).

In the diencephalon, the most densely innervated part of the brain, various nuclei of the anterior and medial hypothalamus, e.g., the suprachiasmatic, supraoptic, paraventricular, arcuate or ventromedial nuclei, as well as of the thalamus, e.g., paratenial and paraventricular nuclei, contain numerous HA fibers (7, 350, 551, 552, 573, 708, 803). Hypothalamic nuclei contain high levels of HA and HDC activity (98, 567), with the latter being decreased after more caudal hypothalamic lesions (232, 233). In the median eminence only, scarce immunoreactive fibers are detected, mainly in the internal layer (7, 350, 351, 551), confirming that the high HA level in this area mainly corresponds to mast cells (567). In the hypophysis, fibers in moderate density occur in the posterior lobe but seem absent in the other lobes (7, 350). Bilateral projections from the TM to widespread regions of the hypothalamus were evidenced by retrograde tracing (701).

Finally, a long descending HA system, also arising from the TM and projecting to various brain stem structures and the spinal cord, was evidenced by lesion (233, 572), immunohistochemical (7, 350, 352, 551, 708, 795), and retrograde tracing studies (207, 632). Interestingly, double tracing studies have suggested that a single TM neuron might send both ascending and descending projections (207), but this is not consistent with other observations (632, 733). Fibers travel caudally in association with the medial longitudinal fasciculus in rats (795) and with the dorsal fasciculus and medial periventricular gray in guinea pigs (7). The most densely innervated structures in the brain stem are the mesencephalic nucleus of the trigeminal nerve, the central gray, the colliculi, and the nucleus of the solitary tract, whereas other cranial nerve nuclei seem less abundantly innervated (7, 350, 352, 572). With the use of antibodies against HA, moderate to dense networks were observed in the substantia nigra and raphe nuclei of guinea pigs (7) as well as of rats (551) in agreement with biochemical (572) but not immunohistochemical data obtained with antibodies against HDC in rats (350). A direct projection of the TM to the locus coeruleus was shown by retrograde tracing (632, 724).

In the cerebellum, irHA fibers are sparsely distributed in all cortical layers and nuclei (7).

In the dorsal horn of the spinal cord (mainly the cervical part), fibers originating from the TM are moderately abundant and some cross the midline (7, 795).

Immunoreactive HA fibers are observed in the wall of intracerebral blood vessels in rats (710) but not in guinea pigs (7).

G. Ontogeny of Histaminergic Neurons

The ontogeny of irHA (35) and irHDC neurons (605) was recently studied in rat brain. The first irHA perikarya were seen on embryonic *day 13* in the border of

metencephalon and mesencephalon and on *day 15* in the ventral mesencephalon, metencephalon, and myelencephalon. From these scattered cells a transient ascending and descending fiber system starts to develop on embryonic *day 15* but has completely disappeared by *day 20*. In contrast, in the basolateral hypothalamus, irHA (35) and irHDC cells (605) were first detected on embryonic *day 16* when they had stopped their mitotic division. The differentiation of immunoreactive neurons in the various subgroups of the caudolateral part of the tuberomammillary nucleus seems largely achieved by embryonic *day 20*, whereas the appearance of the dorsal subgroup in the medial part of the nucleus only occurs during the last prenatal days. Adenosine deaminase is first detected in tuberomammillary neurons on embryonic *day 18* (679).

The development of most irHA fibers takes place during the first two postnatal weeks (35), which coincides with the developmental pattern of HDC activity taken as a selective marker of HA neuronal pool (457).

In contrast, irHA mast cells are most numerous on postnatal *day 4* (when they are mostly located in the hippocampal area), and after that, their number gradually decreases (35), a pattern that explains changes in HA levels, as proposed (457).

H. Afferents to Histaminergic Neurons

Little is known about the sources and biochemical identity of neuronal afferents to HA neurons, namely because their location as a thin sheet of perikarya at the basis of the brain severely restricts the application of retrograde tracing substances. Anterograde tracing studies had shown that substantial projections to the posterior hypothalamus arise from the olfactory tubercle, subiculum, septum, medial preoptic area, and dorsal tegmentum (725), but their actual projections to HA perikarya were not established. Recently, however, Wouterlood and colleagues have started to apply to this problem a double-label immunocytochemical method (826), using antibodies against HDC and *Phaseolus vulgaris* leucoagglutinin, an anterograde tracer. In this way projections from the infralimbic division of the prefrontal cortex (830), all nuclei of the septum diagonal band complex (except the medial and lateral parts of the horizontal limb of the diagonal band) (828), and the medial preoptic region of the hypothalamus (827) were evidenced at the light-microscopic level. The pathways for the afferent fibers could be traced and varicosities on these fibers observed in proximity to irHDC cell bodies and dendrites, suggesting the possible occurrence of synaptic contacts. Because the areas of origin of these afferents receive, in most cases, heavy histaminergic inputs, a reciprocal control with TM neurons was postulated. However, blockade of postsynaptic H_1 and H_2 receptors does not affect HA turnover in cerebral cortex (239).

Afferent serotoninergic and noradrenergic fibers were also described in the TM (207). Although the existence of direct connections remains to be established, the presence of α_2-adrenergic receptors on HA cells (271) may reflect a noradrenergic input.

IV. NONNEURONAL STORES OF HISTAMINE IN BRAIN

Outside the brain mast cells represent a major site of HA storage, and their exposure to antigen (via interaction with immunoglobulin E) or to histamine releasers (e.g., compound 48/80, a basic polymer) leads to extrusion of HA, heparin, and proteases contained in their granules. In peripheral tissues, mast cells are often found in connective tissue, in proximity to vascular elements, and for a long time they were thought to be absent from brain, which contains very little connective tissue. In the early 1970s they were progressively detected by their metachromatic staining by dyes such as toluidine blue (111, 189, 342, 390, 419, 524, 559), and their significant contribution in cerebral HA levels was proposed (457, 654). However, although the existence of this nonneuronal pool of HA is generally admitted, its relative quantitative importance is still debated (328, 584), the function of brain mast cells essentially is unknown (747a), and the existence of additional nonneuronal pools is postulated.

A. Mast Cells in Brain

In peripheral tissues, mast cells are essentially defined by their morphological properties, e.g., metachromasia or alcian blue staining of their very large granules. However, they constitute a heterogeneous population with two main subtypes, the connective tissue and the less typical mucosal mast cell (206). The mast cell subtypes are distinguished by their morphology, staining properties, HA content, composition (e.g., intragranular proteases), and sensitivity to HA releasers (206).

In brain, mast cells, detected by their metachromasia (111, 189, 190, 332, 419, 524, 559), the HA, and in rats 5-HT histofluorescence (199), HA immunoreactivity (7, 550, 552, 707), or their ultrastructure (166, 343), are present in a large number of species (190), including humans (199, 202). Mast cell numbers and localization in brain are characterized by striking variations according to regions, species, individuals, periods of the year, age, sex, side of the brain, and even handling of the animal (for review see Refs. 328, 332, 559, 747a), which may be real or related to the limited reliability of the staining procedure. Nevertheless, from most studies, mast cells seem generally abundant in leptomeninges, pituitary, pineal gland, area postrema, or median eminence but also occur in the brain parenchyma itself, mainly the grey matter, where, similar to their counterparts in peripheral tissues, they are distributed along vessels. The reported number of mast cells in rat brain varies between a few hundreds to >10,000, among which a fraction as large as 80% is found in the thalamus, particularly its lateral nuclei (189, 190, 251, 332, 559). However, in other species the distribution might differ with, for instance, a high density in the cerebral cortex of cats (343) or chimpanzees (190).

The fraction of rat brain HA contained in mast cells has been estimated to be ~50% from lesion and subcellular fractionation studies (231, 457, 654) as well as from mast cell counts combined with HA assays (332); however, others suggested this fraction to be negligible (584). Studies of mutant *W/W*^{v} mice deficient in mast cells did not clarify this issue, because their cerebral HA levels were found to be decreased compared with corresponding controls in two laboratories (447, 793, 833) but not in two other laboratories (335, 528).

A large fraction of HA might be held in mast cells in the neonatal rat brain (457) in which they seem more numerous than in the adult (7, 190, 213). This feature would explain *1*) the relatively high HA level just after birth (555, 619, 669, 749, 836); *2*) the distinct properties of HA-storing granules in neonatal brain, which sediment like those of mast cells (457, 565, 836); *3*) the low turnover of HA, which resembles more that of the amine in typical mast cells than in the adult brain (457); and *4*) the clear in vitro releasing effect of compound 48/80 (457), whereas in the adult brain this effect only occurs with slices of regions, such as the median eminence, where mast cells are abundant (567). Mast cells could proliferate in the neonatal brain under the action of nerve growth factor (11).

Ultrastructural studies (166, 343, 344, 346–348, 713) have all confirmed the close association of brain mast cells with blood vessels and allowed Ibrahim (343) to distinguish two types among these cells. Type I cells are those with morphological properties, including metachromasia, identical to those of typical, i.e., connective tissue, mast cells, which would be those reported by most investigators. Type II mast cells were later called neurolipomastocytes because of the high lipid content of their large granules, which are stained by toluidine blue but are not metachromatic or alcianophilic, although they otherwise display close ultrastructural similarity with typical mast cells. Neurolipomastocytes, which seem more numerous than typical mast cells, enter the brain with pial blood vessels and are always associated with arterioles or venules at the site of vessel branching where autonomic innervation of pial vessels is the densest (166, 713). In these cells, the presence of HA has not been directly demonstrated, but they degranulate under the action of compound 48/80 (166, 347, 348). As mast cells in peripheral tissues (496, 702, 820), neurolipomastocytes in pial arteries of rats and rabbits are autofluorescent cells often situated in apposition with variosities from nerves of sympathetic and other origin, suggesting that their function (secretion?) might be neurally controlled (166, 747a).

Although the function of cerebral mast cells is not established, the localization, innervation, and content of these cells suggest their participation in the regulation of cerebral blood flow and inflammatory reactions (747a).

B. Other Nonneuronal Stores

Histofluorescence studies have suggested the association of HA with cerebral vascular elements (204, 332). In agreement, a relatively high HA level is found in isolated cerebral microvessels in which it is associated with a low HDC content, suggesting that, therein, the amine turns over slowly (362, 381, 382, 616). Because this fraction did not contain metachromatic cells, it was assumed that HA was held in endothelial cells (616), which may contain a still poorly characterized pool of "nascent HA," the formation of which is induced by hormones or various inflammatory agents (370, 646).

The unexpected rise in cerebral HA level that accompanies several large lesions (168, 418) may correspond to this poorly clarified process.

V. HISTAMINE RECEPTORS IN BRAIN

The idea that the various actions of HA on peripheral tissues were mediated by more than one receptor subtype emerged progressively. It was first realized that the antihistamines (now termed H_1-receptor antagonists), the first of which was developed in France in 1937 (87), did not block uniformly all actions of HA, leaving for instance gastric acid secretion unaffected. In 1966, Ash and Schild (31), demonstrating that these various actions could also be differentiated to a certain extent by agonists, clearly postulated the existence of the second (H_2) receptor subtype that was "proven" in 1972 with the development by Black et al. of burimamide (77), the first "selective" antagonist (in the sense that it has no significant affinity for H_1 receptors). Three years later, both H_1 and H_2 receptors were shown to be present in mammalian brain where they control cAMP formation (56, 618) and the firing rate of cortical neurons (279). In 1976, the association of H_2 receptors with adenylate cyclase (298) and that of H_1 receptors with the phosphatidylinositol cycle (361) were shown. Finally, in 1983, Arrang et al. (25) proposed the existence in brain of the H_3 receptor (for which, ironically, burimamide was found to be the most potent antagonist available at this time), which was "proven" in 1987 with the design of fully selective agonist and antagonist compounds (23).

The experimental definition of the three HA receptor subtypes relies on the use of selective agonists and antagonists that are now available, except, however, a highly selective H_1-receptor agonist. Various aspects of the field of cerebral HA receptors were recently reviewed (105, 137a, 256, 304, 305, 658, 659).

A. Histamine H_1 Receptors

1. Molecular properties

The antagonist [^{3}H]mepyramine was introduced in 1977 as the first selective radioligand for H_1 receptors (313) and still displays advantages over other tritiated ligands, i.e., the antidepressants [^{3}H]doxepin (3, 375, 739, 752, 757) or [^{3}H]mianserin (558) as well as (+)-*N*-methyl-4-[^{3}H]methyldiphenhydramine, a quaternary derivative of diphenhydramine (759, 760), that appear less

selective. A mepyramine derivative [^{125}I]iodobolpyramine (78, 414) is also a highly selective probe for the H_1 receptor, which it labels reversibly with high affinity and provides a 50-fold increase in detection sensitivity over [^{3}H]mepyramine (414, 622). Tritiated mepyramine was proposed (589, 591) for H_1-receptor labeling in brains of living mice and as a means of predicting the potential sedating ability of H_1 antihistamines and a variety of antipsychotics and antidepressants (589). This test is currently applied to assess the brain penetration ability of potentially nonsedating H_1-receptor antagonists (6, 109, 429, 620).

The pharmacology of H_1 receptors differs among animal species, since some antagonists, e.g., mepyramine, display significantly lower affinities in rat (or mouse and rabbit) brains than in guinea pig or human brains (3, 73, 117, 120, 121, 306, 311, 377, 414, 755, 797). This rather unusual species difference is confirmed when a functional response, i.e., HA-induced glycogenolysis, is considered (590). The binding of HA to H_1 receptors is inhibited, although to a limited extent, by guanylnucleotides (119, 483, 622), and the effect is lost on solubilization (752). This suggests that the H_1-receptor is regulated by a G protein that is presumably distinct from the N_i protein, because pertussis toxin is inactive on HA binding (483). Sodium ions also decrease HA affinity at H_1 receptors, but the functional significance of this effect is unclear (119). Both thiol-alkylating (240, 834) and the disulfide bond-reducing agents (173–175) stabilize a fraction of the H_1 receptors in a high-affinity state for HA and full agonists, presumably by modifying a critical cysteine residue(s) located outside the HA binding domain (834).

The H_1 receptor can be solubilized using digitonin (240, 243, 752) or other detergents (223, 799). In the solubilized state, it is retained on a wheat-germ agglutinin column, indicating its glycoprotein nature (240), and the molecular sizes of the receptor-detergent complexes determined by gel filtration are 430,000 (752) and 670,000 (223).

The molecular size of the H_1 receptor from various tissues, as determined by target size analysis, ranged from 100,000 to 160,000 (424, 798). A [^{3}H]mepyramine binding site abundant in rat liver membranes has been partially purified, but it does not pharmacologically correspond to the H_1 receptor (223).

A mepyramine derivative [^{125}I]iodoazidophenpyramine is an extremely potent H_1-receptor antagonist (K_D = 10 pM) that, after irradiation, selectively and irreversibly labels a 56-kDa subunit, presumably representing the ligand binding domain of the receptor in guinea pig brain (622, 624) as well as in a variety of other tissues (624). In contrast, the H_1-receptor subunit labeled in heart has a larger apparent mass, suggesting that various tissues may express distinct isoforms of this receptor (622).

2. *Distribution in central nervous system*

The number of cerebral H_1 receptors varies among species but the mean density, i.e., ~100 fmol/mg membrane protein, is in the same range as that of receptors of other neurotransmitters, which are generally more abundant in brain than HA (121, 307, 311, 375, 414, 592, 622, 623). Not only the density of H_1 receptors but also their regional distribution markedly varies between animal species, with, for instance, the cerebellum being the densest area in the guinea pig and the least dense in rat or human brain (121, 375). In human brains, the highest [^{3}H]mepyramine binding is found in the neocortex and various limbic structures (121, 375). These species differences reflect only partly those in histaminergic innervation that appear much less marked (7, 551).

Several cell types might express the H_1 receptor in brain. Kainate lesions decrease H_1 receptors in guinea pig cerebellum, suggesting their association with neuronal membranes (544), but they do not affect them in several areas of rat brain, which may reflect a predominantly nonneuronal localization (122). Although H_1 receptors are present on cerebral microvessels, they represent only a small fraction of the brain's total content (557). The H_1 receptors have also been located on human astrocytoma cells (483).

In contrast, the predominant localization of H_1 receptors to grey matter areas and their highly heterogeneous and sometimes laminar distribution, as established autoradiographically at the light-microscopic level using [^{3}H]mepyramine (543–545) or [^{125}I]iodobolpyramine (86, 414), are consistent with a major neuronal localization.

A detailed atlas of H_1 receptors in guinea pig brain has been established using [^{125}I]iodobolpyramine, which, like other ^{125}I probes, displays distinct technical advantages over ^{3}H probes in autoradiographic studies (86). In the cerebral cortex, H_1 receptors are present in all areas and layers, with a higher density in lamina IV. In the hippocampal formation, H_1 receptors display a laminated pattern of distribution and are the most abundant in the dentate gyrus (hilus and molecular layer) and in several areas of the subiculum and commissural complex. In the amygdaloid complex, the highest densities are found in the medial group of nuclei. In the basal forebrain, the striatum is faintly labeled, whereas the nucleus accumbens, islands of Calleja, and most septal nuclei are highly labeled. In the thalamus, H_1 receptors are present in high density, particularly in the anterior, median, and lateral groups of nuclei. In the hypothalamus the labeling is highly heterogeneous with high densities in, for example, medial preoptic area, dorsomedial, ventromedial, and most posterior nuclei, including the tuberomammillary complex in which histamine perikarya and short axons are present. In the cerebellum the molecular layer is densely labeled (86, 414, 543), but H_1 receptors are also detectable in the granular layer and inner nuclei (86, 414). In normal mice, the pattern is similar, and changes occurring in mutant strains are compatible with a predominant localization to Purkinje cells (621). In guinea pig mesencephalon and lower brain stem, H_1 receptors are particularly abundant in the nuclei of origin of most cranial nerves, in areas containing the perikarya of the catecholamine and 5-HT systems, and in various areas associated with vegetative reflexes,

e.g., the area postrema. The H_1 receptors are abundant in cochlear nucleus in rats (543) and mice (221). In the spinal cord, the highest density is found in the external layers of the dorsal horn in guinea pigs (86) as well as in monkeys (502, 503).

There are several discrepancies between the distributions of HA terminals (7) and H_1 receptors in guinea pig brain (86) that recall similar "mismatches" in other neurotransmitter systems (85, 300, 422). The increase in [^{3}H]mepyramine binding in the developing rat brain parallels that of HDC, a presynaptic marker of HA neurons (134, 720, 756), as well as the HA-induced phosphoinositide hydrolysis (132). Whereas no change in cerebral H_1-receptor density occurs after long-term inhibition of HA synthesis in adult mice (T. T. Quach and J. C. Schwartz, unpublished observations) in newborn rats, their density increases after chronic treatments with a H_1-receptor antagonist (720) and decreases after treatment with an antithyroid agent (134).

3. *Inositol phospholipid hydrolysis*

The observation that responses mediated by H_1 receptors are Ca^{2+} dependent led to the proposition that this receptor subtype was linked to calcium mobilization (656). An early event associated with the stimulation of several calcium-mobilizing receptors is the hydrolysis of inositol phospholipids in the plasma membrane that occurs via activation of the enzyme phospholipase C and releases two types of intracellular messengers: inositol phosphates (inositol 1,4,5-trisphosphate and inositol 1,3,4,5-tetrakisphosphate), which mobilize Ca^{2+}, and 1,2-diacylglycerol, which activates the intracellular protein kinase C (66, 468, 508). Even before general acceptance of the phosphatidylinositol cycle as a major transduction mechanism, it was shown that intracisternal HA accelerates the incorporation of inorganic ^{32}P into inositol phospholipids (220) via H_1-receptor stimulation (719). Meanwhile, mepyramine-sensitive stimulation of phosphatidylinositol turnover by HA was shown to occur in the guinea pig ileum (361). In a more direct study of the initial steps of the cycle, H_1-receptor stimulation was shown to trigger the rapid accumulation of [^{3}H]inositol 1-phosphate in brain slices incubated in the presence of [^{3}H]inositol and Li^+, an inhibitor of inositol 1-phosphatases (65, 97, 115, 116, 131, 158, 159, 173, 386, 831). Other inositol phosphates, i.e., inositol 1,4-bisphosphate and inositol 1,4,5-trisphosphate, are also rapidly accumulated under similar conditions (115, 173, 174). The amplitude of the phosphoinositide response is correlated with the H_1-receptor density in regions of guinea pig brain (115, 158, 159) or during brain development in rats (720). Interestingly, in guinea pig cerebral cortex, the half-maximal concentrations of HA to trigger the phosphoinositide response and the inhibition of [^{3}H]mepyramine are similar (115, 158, 159), and both parameters are similarly reduced by partial irreversible inactivation of H_1 receptors (131). This indicates that the response occurs without any significant receptor reserve, an observation consistent with this response playing a primary role in signal transduction. However, this does not apply to the response in cerebellum on which the effects of partial agonists also suggest a different coupling efficiency (115, 173). The fact that the response to HA is markedly reduced by calcium chelators (115, 386) does not rule out that it is responsible for Ca^{2+} translocation, since this may only reflect the requirement of a minimal Ca^{2+} concentration for phospholipase C activity (353). In cultured vascular smooth muscle cells, H_1-receptor stimulation elicits a transient increase in intracellular Ca^{2+}, which is presumably due to its intracellular mobilization, since it persists in the absence of extracellular Ca^{2+} (459). In contrast with a previous report (695a), H_1-receptor stimulation was also found to increase intracellular Ca^{2+} in neuroblastoma cells, but the response was attributed mainly to the increased entry of extracellular Ca^{2+} and led to hyperpolarization via activation of K^+ channels (517, 518).

Adenosine, despite having no direct effect alone, potentiates the H_1 receptor-mediated hydrolysis of inositol phosphoinositides elicited by HA in guinea pig cerebral cortical slices (308, 309, 321). In contrast, adenosine (385) and GABA (146), which coexist in HA neurons, both inhibit the HA-induced response in slices of mouse and rat cerebral cortex, respectively. Excitatory amino acids also inhibit the HA-induced response in hippocampal slices (54).

4. *Potentiation of adenosine 3',5'-cyclic monophosphate accumulation*

Histamine is among the most powerful stimulants of cAMP accumulation in brain slices (153, 371), and this is attributable to the participation of both H_1 and H_2 receptors in this response (56, 169, 618). Whereas only H_2 receptors are directly linked to the cyclase and the increase in cAMP formation elicited by their activation can be observed in cell-free preparations (298), the effect mediated by H_1 receptors is an indirect one, consists of a large amplification of the cAMP response mediated by H_2 receptors (from a 2- to 3-fold to up to a 15-fold increase), and can be evidenced only in intact cell preparations, such as slices of guinea pig hippocampus conjointly stimulated by H_2-receptor agonists (539). Both H_2 and H_1 receptors mediate the cAMP response to HA in low and high concentrations, respectively. A similar process was shown to operate in slices of rabbit cerebral cortex (8) as well as in vesicular entities (microsacs) of guinea pig cerebral cortex (154, 155, 587).

Stimulation by the H_1 receptor may amplify the cAMP response via one of the two signals known to be generated by the phosphatidylinositol cycle. However, although the H_1 receptor-mediated response is not modified through activation of protein kinase C by phorbol esters (238a), it is significantly reduced in the absence of Ca^{2+} (8, 238b, 661, 666), suggesting that the inositol phosphate branch of the cycle and the Ca^{2+} mobilization that it triggers play a major role. Intracellular Ca^{2+} may activate the adenylate cyclase via interaction with a cal-

modulin-calmodulin binding protein complex in the catalytic subunit of the enzyme.

In a parallel manner, stimulation of H_1 receptors amplifies the cAMP response generated in intact cell preparations by other direct activators of the cyclase, e.g., adenosine (160, 169, 172, 320, 321), catecholamines acting via α-adrenergic receptors (147, 154), or vasoactive intestinal peptide (VIP) (449). The involvement of the products of inositol phospholipid hydrolysis in the potentiation by H_1-receptor agonists of the cAMP response to adenosine was also studied using phorbol esters and a calcium ionophore, but no clear conclusion could be drawn (157, 322, 323).

Baclofen and other $GABA_B$-receptor agonists potentiate the cAMP response induced in rat cortical slices by HA; however, the HA receptor subclass involved was not identified (380). Similar amplifications are found on stimulation of α_1-adrenergic receptors, also linked with the phosphatidylinositol cycle (153, 449).

These amplification processes might be functionally important, inasmuch as they allow enlarged responses to a single transmitter in increasing concentrations as well as mutual potentiations of the responses triggered by two neurotransmitters, e.g., HA and norepinephrine, reaching simultaneously the same target cell. The potentiation between HA and adenosine might also be functionally important in view of a possible corelease of these substances from the same tuberomammillary cells.

5. *Glycogenolysis*

Although less abundant than in liver or muscle, glycogen represents in brain one of the major energy reserves (at least 25% of the total) and may therefore be vital for meeting the high energy expenditure of neuronal activity in the CNS. It is found not only in glial but also in neuronal cells (845). In brain the polysaccharide stores appear to be in a high dynamic state and to be controlled by several neurotransmitters (666). Cerebral glycogenolysis is studied in vivo in the neonatal chick, which lacks a blood-brain barrier (203, 479), or, more conveniently, on brain slices in which levels of [^{3}H]glycogen (synthesized from [^{3}H]glucose) are monitored using a simple assay (590, 595). Glycogenolysis is triggered by norepinephrine (203, 448, 480, 593, 595), histamine (590, 592, 595), adenosine (595), VIP (448), or 5-HT (594). The effect of these various agents is due to phosphorylase activation in the slice preparation (790), which may occur either via cAMP accumulation, e.g., for responses mediated by β-adrenergic (593, 595) or VIP receptors (448), or via translocation of Ca^{2+}, which may activate phosphorylase kinase by binding to its calmodulin subunit (135). The latter mechanism seems to apply to the glycogenolytic response to HA that requires Ca^{2+} in the external medium and is strictly mediated by H_1 receptors (590). An interesting feature of the HA response is that it apparently occurs in a manner similar to that mediated by β-adrenergic receptors (593) with a large receptor reserve (24, 590), which is consistent with the large signal amplification provided by the glycogenolytic cascade. In addition, rapid, selective, and rather large desensitization of the HA response, accompanied by limited changes in [^{3}H]mepyramine binding, can be observed in this system (592).

6. *Guanosine 3',5'-cyclic monophosphate accumulation and other biochemical responses*

Activation of guanylate cyclase and of inositol phospholipid hydrolysis appears to be a related cellular event (66, 318), which may explain why H_1 receptors mediate the HA-induced stimulation of guanosine 3',5'-cyclic monophosphate (cGMP) formation in mouse neuroblastoma cells (609, 611, 738). This response, similar to others mediated by H_1 receptors, requires an intact cell preparation and is Ca^{2+} dependent, suggesting that it is mediated by an increase in intracellular Ca^{2+}, but the latter could not be shown using the fluorescent probe aequorin (695a). In the same preparation, H_1-receptor stimulation triggers arachidonic acid release, possibly via activation of phospholipase A_2, which may indirectly be responsible for the cGMP response (695a). Stimulation of H_1 receptors in blocks of bovine sympathetic ganglia also increases cGMP accumulation (712). Finally, HA-induced cGMP responses were reported using brain slices (153, 425), but the responsible receptor subtype (presumably H_1) was not characterized. Histamine increases [^{3}H]norepinephrine release from brain slices, apparently via H_1-receptor stimulation (717). However, it increases endogenous norepinephrine release via a nonreceptor mechanism (836a).

7. *Electrophysiological responses*

Despite many studies of electrophysiological responses elicited by HA in CNS preparations (for reviews see Refs. 275, 276, 615), those mediated by H_1 receptors are generally not well defined, and their underlying membrane mechanism is poorly understood. One reason is that no highly selective H_1-receptor agonist is available and that many H_1-receptor antagonists have local anesthetic properties, which makes the interpretation of their effects often difficult. Nevertheless, it appears that iontophoretic application of HA to cerebral neurons often leads to excitatory responses when mediated by H_1 receptors. In vivo, osmosensitive neurons in cat supraoptic nucleus, also identified by antidromic invasion from the hypophyseal stalk, increase their firing rate when HA is applied, and this effect is blocked by mepyramine (281, 285). Whereas in cultured supraoptic nucleus neurons no effect of HA was observed (681), excitatory actions of HA, rather well characterized as being H_1 receptor mediated, were observed on acutely prepared explants of the same neurons (19). These excitations mainly occurred in cells either spontaneously active or in which burst activity had been induced antidromically, indicating that they were dependent on electrical activity expressed by the neurons. Although

the underlying membrane mechanism was not studied, it was suggested that HA influenced a voltage-gated conductance via Ca^{2+} translocation.

Other excitatory responses mediated by H_1 receptors occur on cultured tuberal hypothalamic neurons (244, 246) or on hippocampal slices in which slow depolarizations without conductance changes are observed; in addition, on the latter preparation, HA augments excitatory postsynaptic potentials (EPSP) in the CA1 and CA3 areas, presumably via a presynaptic effect (675, 676). In the suprachiasmatic nucleus of slices of rat hypothalamus, local activation of H_1 receptors (similar to that of α_1-adrenergic receptors) inhibits the negative wave elicited by stimulation of the optic nerve (439). On astrocytes of cultured rat brain stem and spinal cord, H_1-receptor stimulation mainly causes depolarizations (325). Excitatory actions of HA after iontophoresis to various brain areas were reported (112, 272, 281, 285, 608), but their possible mediation by H_1 receptors was not shown.

B. *Histamine H_2 Receptors*

1. *Molecular properties*

Until very recently a selective labeling of the H_2 receptor was not achieved because of the limited affinity of available ligands. For instance, the saturable binding of [^{3}H]cimetidine to cerebral membranes was assumed to occur at H_2 receptors (102, 164, 377, 384, 718), but neither the affinity of the tritiated ligand nor the potency of competing agents corresponds to that expected from biological responses mediated by H_2 receptors (613, 693, 800). Tritiated ranitidine (92), [^{3}H]impromidine (665), or [^{3}H]ICIA 5165 (500) also proved to be unsuitable.

The utilization of [^{3}H]HA itself as a ligand has led to complex and somewhat perplexing results. Tritiated histamine binds with high affinity, i.e., with a K_D of 2–10 nM depending on the conditions, to cerebral membranes (43, 149, 542, 663, 704–706, 814) and to gastric mucosal cells (50, 51). In early studies with cerebral membranes, the binding appeared to occur to receptors, as shown by *1*) its sensitivity to guanylnucleotides, *2*) its neuronal localization suggested by the effects of kainate lesions, *3*) its marked regional heterogeneity, and *4*) its localization to synaptosomal membranes (43, 542). However, whereas histaminic drugs were active as competing agents, their potencies did not correspond to those at either H_1 or H_2 receptors (or at H_3 receptors that were not yet identified at this time), and it was suggested that the binding occurred at one of the HA receptors in the desensitized state. More recently in an extensive study in which binding parameters were widely varied, several components were distinguished, among which was one characterized by potencies of agonists (but not antagonists) corresponding to those at H_2 receptors. It was proposed that the binding occurred to an allosteric site of the H_2 receptor, but this remains to be established in functional studies (704–706). Whatever the site to which [^{3}H]HA binds, the ligand cannot be used to reliably label the H_2 receptor in biochemical or autoradiographic studies.

Although in several laboratories the antagonist [^{3}H]tiotidine had not been found suitable for labeling the H_2 receptor (49, 52, 442, 666), with the use of a more purified batch of the tritiated ligand, a fraction (~30–40%) of its binding to membranes of guinea pig brain (225, 364, 510, 612, 694, 711) or lung (217) apparently occurred to H_2 receptors, as judged from the potencies of antagonists. In contrast, the K_i values of HA and agonists were 10- to 100-fold higher than their half-maximal inhibitory concentration (IC_{50}) for biological responses mediated by H_2 receptors (including adenylate cyclase activation), implying that the latter occurs with a very large receptor reserve (225). Although significant binding could be detected in three brain areas (cerebral cortex, striatum, hippocampus), this was not the case for other areas or peripheral tissues known to contain H_2 receptors, presumably due to a high nonspecific binding.

More recently, [^{125}I]iodoaminopotentidine, a ^{125}I antagonist, was designed as a highly potent (K_D = 0.3 nM), sensitive, and selective ligand for H_2 receptors (624a, 754a). With this probe the nonspecific binding represented <20–30%, which allowed it to be used not only in biochemical but also in autoradiographic studies (456a, 624a). The corresponding azido derivative was designed as a photoaffinity probe for the H_2 receptor and was shown to bind irreversibly to 58- and 32-kDa peptides isolated by electrophoresis. The H_2-receptor ligands prevented the labeling of these peptides, which were therefore identified as containing the HA recognition domain of the H_2 receptor (624a).

2. *Adenylate cyclase activation*

Several years before the definition of H_2 receptors and the design of selective antagonists, HA was shown to stimulate adenylate cyclase in broken cell preparations from guinea pig heart, and this effect was shown to be blocked by antihistamines in concentrations well above those required for interaction with H_1 receptors (398, 432, 465). As summarized (153, 487), in brain, most early studies were performed with slices in which the responses are much larger than in membranes, e.g., in rabbits (218, 371), guinea pigs (686), rats (653) or humans (409, 687), but they are more complex since, with the exception of the chick (481, 482), they do not involve a single receptor (see sect. V*A4*).

However, despite its limited stimulation (2- to 3-fold) on cell-free preparations from guinea pig hippocampus, a HA-sensitive adenylate cyclase could be characterized biochemically and pharmacologically as being selectively linked to the H_2 receptor (257, 298, 333, 379). Although rat brain adenylate cyclase is much less sensitive to HA than is guinea pig, some stimulation was reported (257, 298, 548, 580). In several peripheral

tissues, e.g., heart or stomach, where biological responses mediated by H_2 receptors occur, a HA-sensitive adenylate cyclase, also selectively linked to the H_2 receptor, was characterized (for review see Ref. 363). Furthermore, a number of H_2 receptor-mediated responses are mimicked by cAMP analogues and potentiated by phosphodiesterase inhibitors, suggesting that cAMP is the universal second messenger of HA at H_2 receptors.

The enzyme is activated by HA, which, in rather low concentration ($EC_{50} = 10\ \mu M$), increases its maximal reaction velocity without altering the K_m for its substrate Mg-ATP. The nucleotide guanosine triphosphate stimulates the enzyme and markedly potentiates the HA-induced stimulation, indicating that the ternary model (617) comprised of the H_2 receptor (the HA recognition subunit), a GTP regulatory protein (G_s) (the transducer), and adenylate cyclase (the catalytic unit) applies to this system. Free Mg^{2+} stimulates the catalytic activity presumably by interacting with an allosteric site of the enzyme, the affinity of which might be increased on HA stimulation (379).

The adenylate cyclase response in membranes of guinea pig brain is triggered by H_2-receptor agonists and competitively inhibited by typical H_2-receptor antagonists at concentrations closely consistent with those required at H_2 receptors mediating various biological responses (257, 298). However, an intriguing observation is that a series of psychotropic compounds, namely several neuroleptics and a number of structurally diverse antidepressants, behave as extremely potent and competitive inhibitors of the response to HA on cerebral membranes (257, 259, 378). This has led to the suggestion that blockade of the H_2 receptor represents the molecular basis of clinical antidepressant activity (378). However, on intact cell preparations, i.e., hippocampal slices (156) or dissociated brain tissues (374), stimulated by selective H_2-receptor agonists, these compounds are relatively weak antagonists. The reasons for these intriguing differences are not known, and stimulation of adenylate cyclase in membranes should not be regarded as a reliable system to assess the activity of compounds at H_2 receptors. In addition, the idea that antidepressants derive their clinical efficacy from blockade of cerebral H_2 receptors seems unlikely, particularly since such a blockade could not be observed after chronic treatments (514).

In several systems increased intracellular cAMP content leads to final biological responses via enhanced phosphorylation of intracellular proteins. However, although stimulation of H_2 receptors in gastric parietal cells was shown to selectively activate a cytosolic type I cAMP-dependent protein kinase (124) and to stimulate the phosphorylation of several cytosolic proteins (125, 451), the corresponding effects on cerebral H_2 receptors were not reported. These intracellular steps mediated by cAMP might be regulatory steps, because electrophysiologically hypersensitive responses to HA elicited by denervation (286) or chronic antidepressant treatments (514) are not accompanied by changes in responsiveness of the cAMP system to HA.

3. *Phospholipid methylation and other biochemical responses*

Hirata and Axelrod (316) suggested that methylation of membrane phospholipids plays a role in signal transduction across membranes. Stimulation of H_2 receptors in mast cell membranes (754) and synaptic membranes of rat brain (536, 537) rapidly increases incorporation of [^{3}H]methyl groups from *S*-[^{3}H]adenosylmethionine into phospholipids. On the latter preparation, the EC_{50} of HA was 5 μM, and concentration-response curves obtained with several agonists and antagonists rather clearly identified the H_2 receptor as mediating the response. Although controversial (836a), release of endogenous norepinephrine might be modulated by H_2 receptors (79a). The absence of correlation between the density of binding sites and adenylate cyclase activity (624a) might reflect the existence of H_2-receptor subtypes, possibly linked to these various responses.

4. *Localization*

Until recently the information on H_2-receptor localization in the brain was essentially derived from studies of the cAMP response they mediate. The fact that this response occurs in neurons is suggested by several observations: *1*) the HA-sensitive adenylate cyclase is enriched in synaptic membranes isolated from guinea pig cerebral cortex (379); *2*) the cAMP response occurs on various fractions enriched in neuronal elements, e.g., the vesicular sacs called synaptoneurosomes (229, 230, 322, 323, 548, 586, 587); and *3*) kainate lesions in the hippocampus nearly abolish the response in slices (234), whereas interruption of HA afferents does not affect it (286). The prenatal development pattern of the cAMP response is also consistent with a neuronal localization of H_2 receptors (689).

The cAMP response involving H_2 receptors is not limited to neurons, since it can be also evidenced in human astrocytoma cells (129), epithelial cells of choroid plexus (148), and cerebral microvessel preparations (341, 367, 382, 546, 547). However, a clear cAMP response can only be measured in a few brain areas of a few animal species, and the amplitude of the response (153, 670) does not parallel the relative densities of histaminergic afferents, which suggests that mismatches exist for not only H_1 but also H_2 receptors.

In contrast with binding data obtained with [^{3}H]iodotidine (612, 694), autoradiographic mapping of the H_2 receptor in guinea pig or rat brains using ^{125}I-aminopotentidine has shown it to be distributed widely and in a highly heterogeneous fashion, e.g., with clearcut differences among laminae of cortical areas, suggesting its major association with neurons (624a).

The H_2 receptors are present in most areas of the cerebral cortex, with the highest density in the superficial layers, the piriform and occipital cortex, which contain low H_1-receptor density. The caudate putamen (which contains low H_1-receptor density), nucleus accumbens, and olfactory tubercles are among the richest

brain areas. In the hippocampal formation, H_2 receptors display a laminated pattern with dense labeling in the lacunosum moleculare, radiatum, and oriens layers. In the thalamus the low density of H_2 receptors contrasts with the high density of H_1 receptors. The H_2 receptors are not abundant in the hypothalamus (where HA axons are the densest) nor in most other brain areas except the superficial gray layer of colliculus superior and, to a lesser extent, the substantia nigra. These distributions suggest that H_1 and H_2 receptors may mediate together the actions of HA in certain brain areas, e.g., cerebral cortex or hippocampus, whereas in other areas, e.g., thalamus or caudate putamen, a single subtype might be primarily involve. The H_2 receptors are hardly detectable in pituitary.

5. Electrophysiological responses

In early studies in which HA was applied by microintophoresis on many neurons all over the CNS of anesthetized animals, the response most frequently found was an inhibition of firing, with both fast onset and fast recovery (for review see Refs. 276, 277). This pattern was found on neurons from the cerebral cortex (279, 285, 563, 564, 639), the brain stem reticular formation (89, 278), the dorsal raphe nucleus (427, 428), the cerebellum (458, 690), the vestibular nucleus (391, 641), the thalamus and hippocampus (273, 285), the ventromedial nucleus of the hypothalamus (608), and the preoptic area (112). These depressive actions may be mediated by H_2 receptors, as suggested in some of these studies by the blockade exerted by burimamide, metiamide, or cimetidine. However, this conclusion is only a tentative one, since *1)* the iontophoretic application does not allow one to determine the apparent affinities of antagonists, *2)* metiamide and even more burimamide are now known to display very significant H_3-receptor antagonist potency, and *3)* the highly selective H_2-receptor agonists dimaprit and impromidine were generally not tested.

Iontophoretically applied metiamide also antagonizes, at least partly, the depressant responses of cerebral cortical neurons elicited by stimulation of the medial forebrain bundle, of hippocampal cortical neurons elicited by stimulation of the fornix (284, 285, 640), or of nucleus accumbens neurons evoked by stimulation of the afferent fimbria (126). These various data suggest that H_2 receptors mediate the inhibitions elicited by endogenous HA, a view supported by the clear hypersensitive inhibitory response that develops in the guinea pig sensorimotor cortex after lesions of the ascending HA pathway (286).

On unidentified cells of explants of tuberal hypothalamus, iontophoretic application of HA also elicits depressant effects with a rapid time course, which are clearly mediated by H_2 receptors; furthermore the persistence of the response in a Ca^{2+}-free medium and its potentiation by phosphodiesterase inhibitors suggest that it is postsynaptically mediated by an increase in cAMP (245, 246). Histamine hyperpolarizes human spinal neurons in culture (588). A similar effect is mediated by H_2 receptors on astrocytes of cultured rat brain stem and spinal cord (326) and on suprachiasmatic neurons of rat hypothalamic slices (439).

In slices of rat hippocampus, local pressure or iontophoretic application of HA or impromidine to pyramidal or granule cells hyperpolarizes these cells via a presumably postsynaptic effect (273). Perhaps more important effects, apparently mediated by H_2 receptors, were evidenced on the same preparation by Haas and colleagues (274, 276, 280, 282, 283) when HA or impromidine was added to the perfusion fluid and when CA1 pyramidal neurons were recorded intracellularly. Histamine caused a slight depolarization without change in resting membrane conductance, an abbreviation of long afterhyperpolarizations, and a loss of accommodation of action potential firing to excitatory inputs. The two latter actions result in a strong potentiation by HA of various excitatory signals, e.g., depolarization induced by excitatory amino acids and synaptically evoked spikes, by inhibition of their self-restriction processes. These effects were attributed to a decrease of a Ca^{2+}-activated K^+ conductance (283), a mechanism confirmed by voltage-clamp studies (556) and that may also underly the action of HA at medullary (90, 366) or myenteric neurons (490). A similar mechanism might be responsible for the H_2 receptor-mediated enhancement of excitability of CA3 pyramidal neurons treated with penicillin (523) or after stimulation of mossy fibers (729). These indirect excitatory effects might depend on intracellular cAMP inasmuch as they are potentiated by a phosphodiesterase inhibitor and mimicked by intracellular application of the nucleotide (275) or activation of the cell's adenylate cyclase by forskolin (499).

Abbreviation of afterhyperpolarization in the same cells triggered by stimulation of β_1-adrenergic receptors also occurs via a similar mechanism (499). A similar effect elicited by stimulation of muscarinic receptors (59) might result from intracellular protein kinase C activation (39). Therefore it appears that inhibition of a Ca^{2+}-dependent K^+ conductance might represent the final common path for the actions of various neurotransmitters released from several highly divergent neuronal pathways. Hence, as underlined (276), these essentially modulatory actions of HA, consisting of a weak direct effect but a strong potentiation of excitatory signals, suggest that the function of the amine in brain is not to transmit discrete information but to regulate in a coordinate manner the excitability of large cerebral areas (655, 660).

C. Histamine H_2 Receptors

1. Molecular properties

The highly potent agonist R-α-[^{3}H]methylhistamine (MeHA) constitutes a suitable probe for the selective labeling of the H_2 receptor (23). In the absence of divalent cations, R-α-[^{3}H]MeHA binds in a saturable

manner to an apparently homogeneous population of sites in membranes of rat cerebral cortex. The binding is reversible, as indicated by the similar dissociation constants (K_D = 0.8 nM) derived from either association-dissociation kinetics or saturation kinetics at equilibrium (K_D = 0.4 nM). These binding sites are pharmacologically identified as H_3 receptors by competition studies performed with various H_1, H_2, or H_3 histaminergic drugs (28a). The relative potencies of various agonists and affinity constants of various antagonists are highly correlated with the corresponding values obtained at functional H_3 autoreceptors regulating HA release or synthesis. For instance, the *R*-isomer of α-MeHA is ~10 times as potent as HA itself, and *S*-α-MeHA is ~100 times less potent than *R*-α-MeHA. This confirms that enantiomer corresponding to *S*-configurated L-histidine are highly preferred at H_3 receptors, whereas enantiomers corresponding to D-histidine are more potent at H_2 receptors, with no difference being observed at H_1 receptors (23, 29). The potent and specific H_3-receptor antagonist thioperamide (23), the H_1-receptor agonist betahistine (24), the H_2-receptor agonist impromidine (25), and the psychoactive drug phencyclidine (21) inhibit *R*-α-[^{3}H]MeHA binding with the same affinity as that displayed when tested as antagonists at functional H_3 autoreceptors.

Two affinity states of the H_3 receptor are observed when the binding of *R*-α-[^{3}H]MeHA is studied in the presence of Ca^{2+} in physiological concentrations, an effect that is not reproduced by Mg^{2+} and apparently arises from the conversion of a major fraction of H_3 receptors to a lower affinity state (K_D = 16 nM). The binding of the tritiated ligand to this low-affinity component is entirely and specifically inhibited in the presence of guanylnucleotides, indicating that the H_3 receptor is coupled to its (so far unknown) effector system via a G protein. However, at numerous other receptor types, guanylnucleotides affect binding to the high- and not the low-affinity component (28a). The low-affinity component may correspond to the functionally active receptor, since the K_D value of *R*-α-MeHA at this component is close to its EC_{50} values at H_3 autoreceptors regulating HA release and synthesis. However, the functional involvement of the high-affinity population of sites cannot be entirely excluded, since it also appears to be (although very partially) GTP regulated. The 10 times higher affinity of agonists to this high-affinity component compared with their potency in functional studies suggests that these sites may represent the H_3 receptor in a modified (desensitized?) state.

2. *Distribution in central nervous system*

The mean density of cerebral *R*-α-[^{3}H]MeHA binding sites determined in physiological conditions in rats is rather low, i.e., ~30 fmol/mg membrane protein. It is slightly higher in the guinea pig brain, suggesting that the number of H_3 receptors, similar to that of H_1 receptors, varies among species. The H_3 receptors mediate the autoinhibition of HA release in human brain with a pharmacology apparently similar to that of corresponding receptors in rodents (22).

The distribution of H_3 receptors in rat brain, established from either membrane binding studies or autoradiographic studies, is highly heterogeneous (23; H. Pollard, J. Moreau, J. M. Arrang, and J. C. Schwartz, unpublished observations; Fig. 2).

In cerebral cortex where they are rather dense, H_3 receptors are found in all areas and layers with, however, a higher abundance in rostral areas and in laminae IV and V. In the hippocampal formation, they are moderately to highly abundant, with their density being the highest in the dentate gyrus, moderate in subiculum, and very low in the fimbria. In the amygdaloid complex high densities are found in central, lateral, and basolateral nuclei as well as in the bed nucleus of the stria terminalis, which contains a dense histaminergic innervation (60).

In the basal forebrain, numerous H_3 receptors are present in anterior olfactory nuclei, nucleus accumbens, and olfactory tubercles, as well as in striatum, particularly in its dorsomedial part; they are less numerous in the globus pallidus and even less in the septum. In the thalamus, H_3 receptors are mainly detected in various midline, intralaminar, and lateral nuclei. In the hypothalamus, their moderate density contrasts with the high density of HA axons, but they are detectable at the level of the tuberomammillary nucleus where they may reside on perikarya or dendrites (28). In the mesencephalon, they are numerous in the substantia nigra, particularly in its pars reticulata, the ventral tegmental area, and superior colliculi. In cerebellum, low densities are present in all layers. In the brain stem, they are mainly present in pontine nuclei, around the fourth ventricle, in locus coeruleus, and in the dorsal tegmental nucleus. In the spinal cord, a low density is present mainly in external layers of the dorsal horn.

This distribution of H_3 receptors, not strictly parallel to that of histaminergic axons, suggests that they are not restricted to the latter. This is confirmed by the identification of H_3 receptors on serotoninergic and noradrenergic nerve terminals in the cerebral cortex (652, 652a) and a cerebral vessel (197). Their decrease elicited in striatum by local administration of the neurotoxin kainate is consistent with a major neuronal localization (Pollard et al., unpublished observations).

In the vegetative nervous system, H_3 receptors with a presynaptic localization have been evidenced at the level of the mesenteric artery where they mediate inhibition of excitatory junction potentials generated by stimulation of sympathetic perivascular nerves (354). Also, their stimulation inhibits transmission at nicotinic synapses of enteric ganglia (737), an effect that may be responsible for the inhibition of electrically evoked contractions of the ileum (762). Presynaptic H_3 receptors on vagal nerve endings might also be responsible for the inhibition of cholinergic transmission in airways (348a, 349) and of gastric acid secretion (301, 302). Presynaptic H_3 receptors might also mediate inhibition of neuropep-

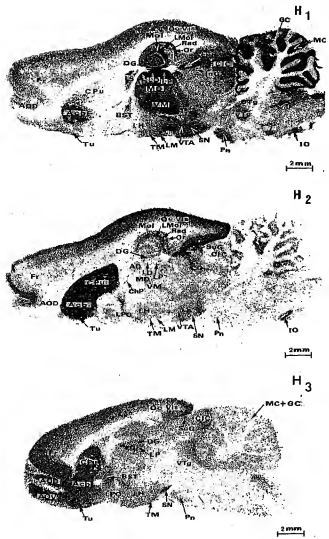


FIG. 2. Autoradiographic localization of histamine receptors on midsagittal sections of brain. H_1 and H_2 receptors were visualized on sections of guinea pig brain using [^{125}I]iodobolpyramine and [^{125}I]iodoaminopotentidine, respectively. (Courtesy of M. L. Bouthenet.) H_3 receptors were visualized on section of rat brain using R-α-[^{3}H]methylhistamine. Abbreviations: ACb, nucleus accumbens; AD, anterodorsal thalamic nucleus; AOD, anterior olfactory nucleus, dorsal part; AOV, anterior olfactory nucleus, ventral part; BST, bed nucleus of stria terminalis; CIC, central nucleus of inferior colliculus; CG, central gray; ChP, choroid plexuses; CPu, caudate putamen; DG, dentate gyrus; DTg, dorsal tegmental nucleus; Fr, frontal cortex; GG, granular layer of cerebellum; InG, intermediate gray layer of superior colliculus; IO, inferior olive; LD, laterodorsal thalamic nucleus; LH, lateral hypothalamic area; LM, lateral mammillary nucleus; LMol, lacunosum molecular layer of hippocampus; LP, lateral posterior thalamic nucleus, LPO, lateral preoptic area; LS, lateral septum; MC, molecular layer of cerebellum; MD, mediodorsal thalamic nucleus; Mol, molecular layer of hippocampus; Oc Vis, occipital visual cortex; Or, oriens layer of hippocampus; Pn, pontine nuclei; Rad, stratum radiatum of hippocampus; SN, substantia nigra; SuG, superficial gray layer of superior colliculus; TM, tuberomammillary nucleus; Tu, olfactory tubercle; VM, ventromedial thalamic nucleus; VPA, ventral tegmental area; VTg, ventral tegmental nucleus; 7, 7th cranial nerve.

tide release from airway sensory nerves (348b, 348c). Hence H_3 receptors are not restricted to the brain.

3. *Actions mediated by H_3 receptors*

The best established actions mediated by H_3 receptors are the presynaptic inhibitions of release of several neurotransmitters, i.e., HA, 5-HT, and norepinephrine in the brain and possibly acetylcholine, norepinephrine, and neuropeptides in the peripheral nervous system. As in the case of other presynaptic receptors, these actions may arise from a restriction of Ca^{2+} influx related to increases in hyperpolarizing conductances, possibly mediated by changes in channel phosphorylations resulting from inhibition of adenylate cyclase (511).

Stimulation of H_3 receptors decreases wakefulness in cats (369, 437a) and spontaneous motor activity in rats (93). It induces vasodilation of the rabbit isolated middle cerebral artery (197).

Nonneuronal (mast cell?) H_3 receptors mediate the inhibition of HA synthesis in various peripheral tissues (23).

VI. ROLE OF HISTAMINERGIC NEURONS IN NEUROENDOCRINE CONTROLS

Both the morphology of HA perikarya, recalling that of magnocellular secretory neurons in the anterior hypothalamus, and the high density of their projections to hypothalamic areas involved in the regulation of hormonal secretions are consistent with a participation of endogenous HA in neuroendocrine controls. In agreement with this hypothesis, exogenous HA elicits a variety of hormonal responses in vitro or in vivo, but the role of endogenous HA has been difficult to demonstrate (for reviews see Refs. 178, 179, 770, 810).

Systemic administration of HA elicits marked biological responses, such as hypotension or adrenal hormone secretion, which in turn may indirectly affect neuroendocrine controls. Because such changes may not involve histaminergic systems in the brain, they are generally not considered here.

A. *Posterior Pituitary Hormone Secretion*

Both the supraoptic and paraventricular nuclei of the hypothalamus, which synthesize and control the release of vasopressin and oxytocin, contain high levels of HA (98) and HDC activity (567) and high densities of HA axons (551). The neurohypophysis itself contains, mainly in its peripheral part, HDC- and HA-immunoreactive fibers, presumably arising from the TM and passing through the internal layers of the median eminence and the infundibular stalk (351). The H_1 receptors are extremely abundant in the supraoptic nucleus and present in the paraventricular nucleus (86, 543).

In several animal species, intracerebroventricular administration of HA elicits antidiuretic responses (61,

69, 71, 317, 431, 772, 773), which seem to result from increased vasopressin secretion (69, 71, 171, 775, 776). The effects of various agonists and antagonists indicate that this action is selectively mediated by H_1 receptors (61, 317, 776).

Iontophoretic application of HA to the supraoptic nucleus increases the firing of the neurosecretory cells also via H_1 receptors, but the possibility of a distal effect was raised (285), and no effects were observed by others (45, 631). In perfused rat hypothalamoneurohypophyseal explants, HA excited and facilitated the burst activity of antidromically stimulated supraoptic neurons; the effects occurred via H_1 receptors and appeared to depend on the electrical activity of the neuron, suggesting that HA affected a voltage-dependent conductance (19).

Although the effects of exogenous HA seem well established, this is not the case for a possible participation of the endogenous amine in the control of vasopressin release. In Brattleboro rats genetically lacking vasopressin, the HA levels are elevated in several hypothalamic nuclei, including the supraoptic nucleus, and decreased in the neurohypophysis, but the functional significance of these findings is obscure (139). Pituitary vasopressin depletion induced by repeated administrations of hypertonic saline was accompanied by a significant decrease in HA levels in neurohypophysis (785), suggesting that the control of vasopressin secretion by HA might occur at the level of both perikarya and terminals of the neurosecretory neurons. Increased hypothalamic HA, induced by chronic His loads in rats, decreased vasopressin levels in the anterior hypothalamus but did not modify the hormone level in plasma; chronic inhibition of HA synthesis by α-FMH impaired the vasopressin response to adrenalectomy but did not modify significantly vasopressin secretion in controls (107). Hence HA neurons might control vasopressin secretion under certain circumstances, but since changes in basal secretion do not occur after HA depletion and were never reported after administration of H_1-receptor antagonists alone, endogenous HA may not exert a tonic influence on neurosecretion under basal conditions.

The secretion of oxytocin is also enhanced after intracerebroventricular administration of HA, but high doses are necessary (171).

B. Prolactin Secretion

Secretion of this hormone by the lactotrophs of the adenohypophysis is mainly controlled, in a tonic inhibitory fashion, by dopamine released from tuberoinfundibular neurons into the median eminence capillaries of the portal system. There are various indications that HA might be involved in the control of prolactin secretion.

Intracerebroventricular administration of HA in male or ovariectomized estradiol-primed rats increases the plasma levels of prolactin (18, 176, 180, 184, 435, 614). Intravenous HA elicits similar responses in steroid-primed rats (614), in rhesus monkeys (193), and in human males (400, 406, 578). This effect does not appear to be exerted at the level of the anterior pituitary, because it is not observed after local injections or applications of HA (435, 614). The anterior pituitary does not contain irHA axons (351), and H_1 or H_2 receptors appear scarce (M. L. Bouthenet, unpublished observations).

Histamine may act on central structures in the vicinity of the third ventricle, because the threshold doses of the amine are lower when given in the ventricle than in the lateral ventricle or systemically (178) and because prolactin secretion is also elicited by HA administered into the anterior hypothalamic area or the arcuate nucleus region (13, 15, 435). Histamine infused centrally decreases the secretion of dopamine into the pituitary portal blood of female (248) and male rats (404, 405). Dopamine receptor blockade by pimozide did not prevent the rise in plasma prolactin elicited by intracerebroventricular administration of HA (404). Hence the prolactin-stimulating effect of HA might occur through an inhibition of the tuberoinfundibular dopaminergic neurons. Both the arcuate nucleus and the median eminence contain irHA and irHDC axons (351) and H_1 receptors in moderate density (86, 543, 681). Receptor antagonists for 5-HT partially prevent the action of HA, suggesting a participation of the endogenous indolamine (405). The rat median eminence, which is located outside the blood-brain barrier, also contains mast cells depletable by compound 48/80 (567), and injection of this compound systemically, but not intraventricularly, increases prolactin secretion (182).

The receptor subtypes mediating the effect of HA have been subject to some controversy (for detailed discussion see Refs. 177, 178). The rise in prolactin secretion elicited by HA in rats is blocked by various H_2-receptor antagonists injected intracerebroventricularly (183, 185, 186, 400, 402, 403) and mimicked by dimaprit, a selective H_2-receptor agonist (186, 401). However, dimaprit was also shown to reduce plasma prolactin (186, 209). Intra-arterial administration of cimetidine or ranitidine, two H_2 antagonists that do not cross easily the blood-brain barrier, partially blocked the effect of intracerebroventricularly administered HA (403).

A possible participation of H_1 receptors in the HA-induced secretion of prolactin is less clear than that of H_2 receptors. The H_1-receptor antagonists, such as mepyramine, that easily cross the blood-brain barrier (591) partially block the effect of centrally administered HA when they are administered intracerebroventricularly in relatively high dosages (180, 403) but do not block it when administered intravenously (405). Hence a nonspecific effect of the H_1-receptor antagonists administered centrally, e.g., via membrane stabilization, seems likely. In contrast, systemically administered H_1 antagonists appear to block the prolactin secretion induced by intravenous HA, but the latter effect might be indirect and not mediated by cerebral receptors (406, 443, 614).

A possible role of endogenous HA in the control of prolactin release under various circumstances was investigated using receptor antagonists or a synthesis in-

hibitor as pharmacological tools. The H_1-receptor antagonists administered systemically do not modify basal prolactin secretion in male rats (403) or in humans (406). In contrast, the H_2-receptor antagonist cimetidine, given intravenously, promotes prolactin secretion in humans (104, 114, 406) or in rats (492), and chronic treatments with the drug produces gynecomastia and galactorrhea accompanied by hyperprolactinemia in a few patients (48, 163). These observations would not be consistent with a role of HA in promoting prolactin secretion via H_2-receptor stimulation, but other observations suggest that the effect of cimetidine is not related to H_2-receptor blockade. Hence the effect of cimetidine was not modified by the H_2 agonist impromidine (681); in addition, ranitidine was less effective than cimetidine, although it is a more potent H_2 antagonist, and oxmetidine, another H_2 antagonist, seems completely ineffective (407, 492, 683). Finally, a compound resembling cimetidine in chemical structure but devoid of H_2-antagonist activity stimulated prolactin secretion (402). Because most H_2 antagonists do not easily cross the blood-brain barrier, it will be of interest to assess the action of the brain-penetrating antagonist zolantidine (108).

Depletion of hypothalamic HA by α-FMH (235) is accompanied by a decrease in basal plasma prolactin levels (495).

The rises in plasma prolactin elicited in male rats by restraint stress or acute exposure to ether vapors is prevented by several H_2 antagonists administered intracerebroventricularly as well as by α-FMH (12, 403, 495, 678). The H_1 antagonists administered systemically partially decrease the prolactin responses (12, 403). In contrast, the prolactin response triggered by suckling of lactating rats or by estrogens is blunted by H_1 antagonists but is not affected by H_2 antagonists (13, 18).

Taken together and despite several inconsistencies, these various studies suggest that cerebral histaminergic neurons participate in the control of prolactin secretion with a major involvement of H_2 receptors, but the participation of H_3 receptors remains to be assessed.

C. *Thyrotropin Secretion*

Thyrotropin (TSH) secretion by the adenohypophysis is controlled in a stimulatory fashion by thyrotropin-releasing hormone (TRH), a tripeptide released by neurons originating from the paraventricular and periventricular nuclei of the hypothalamus and ending in the external zone of the median eminence in apposition with the capillaries of the portal system. On the contrary, somatostatin, released at the same level from neurons originating from the periventricular area, inhibits TSH secretion.

Histamine might be involved in control of TSH secretion (for review see Ref. 765).

Intracerebroventricular administration of HA does not change basal TSH secretion (319, 443, 768) but decreases TSH secretion induced by either exogenous TRH (768) or by a cold stress (764, 766, 768, 769). Furthermore, His, in doses large enough to increase cerebral HA (668), inhibits the cold-stimulated (but not the TRH induced) TSH response, suggesting a role for endogenous HA (769). From the effects of focal injections, HA appears to act at the level of the periventricular hypothalamus (768) and not of the pituitary, since the amine did not modify basal or TRH-stimulated release of TSH from superfused rat anterior pituitary cells (767) and since dimaprit did not modify TSH release from anterior pituitary halves in vitro (167). The inhibition of the cold response by HA cannot be ascribed to an impaired release of TRH, since the amine actually liberates TRH from hypothalamic slices (123, 368) or synaptosomes (62), with both effects being apparently mediated by H_2 receptors. Theoretically the action of HA might result from somatostatin release, but this effect is not substantiated by experimental evidence. It is not clear whether the effect of HA on the cold response is receptor mediated since it was mimicked by impromidine or 2-pyridylethylamine but not antagonized by either mepyramine or cimetidine (768, 769). In contrast, systemic administration of the selective H_2 agonist dimaprit reduced serum TSH basal level in a cimetidine-reversible manner (167).

Furthermore, mepyramine and cimetidine administered alone do not modify the cold-induced secretion of TSH (768), suggesting that endogenous HA is not involved.

D. *Growth Hormone Secretion*

Growth hormone (GH) secretion is controlled in opposite fashions by GH-releasing factor (GRF) and somatostatin.

In unanesthetized male rats, intracerebroventricular administration of HA suppresses the spontaneous pulses of GH secretion, and this effect is partially mimicked by an inhibitor of HMT (491). This effect was not observed in rats in which most of the somatostatinergic innervation of the median eminence was eliminated (372), which may suggest that HA triggers somatostatin release. However, a somatostatin antiserum did not prevent the suppression of GH pulses by HA (493).

In anesthetized dogs, intracerebroventricular HA reduces GH secretion only slightly (625). In rats, HA also diminishes the GH secretion elicited by morphine, an action apparently mediated by H_1 receptors (494). Intracerebroventricular administration of GRF in low dosage elicits significant increases in HA concentrations in rat hypothalamus and pituitary, whereas somatostatin elicits opposite changes (106). These observations suggest reciprocal interactions between somatotropinergic and histaminergic systems in brain, but their relevance to the regulation of GH secretion remains to be clarified.

E. *Adrenocorticotropic Hormone Secretion*

For a long time, a role for HA in the control of adrenocorticotropic hormone (ACTH) secretion has

been postulated from the numerous observations showing that, on systemic administration, it elicits increases in plasma ACTH and corticosterone levels mainly via stimulation of H_1 receptors (178, 770, 810). In addition, various stressful procedures affect HA turnover in brain (see sect. XIII1A). However, a participation of cerebral histaminergic neurons in the control of ACTH secretion largely remains to be clarified, since stimulation of peripheral H_1 receptors causes hypotension, a strong stimulus for ACTH secretion.

Intracerebroventricular administration of HA in doses low enough to avoid stimulation of peripheral receptors increases ACTH and/or corticosteroids secretion in both dogs (625) and rats (99, 101, 677) in which it is accompanied by an increased secretion of β-endorphin (399). In rats, H_1 receptors alone (677) or together with H_2 receptors seem involved (99, 101), whereas in dogs 4-methylhistamine, a predominantly H_2-receptor agonist, decreases ACTH secretion (625). The action of HA does not appear to result from a direct secretory effect on either corticotropin hormone-releasing hormone (210, 314) or ACTH (630), as indicated by in vitro studies with hypothalamic and pituitary tissues, respectively. Hence an indirect action through other monoamines controlling ACTH secretion has been suggested (100, 600). However, iontophoretically applied HA strongly excites cortisol-inhibitable neurons in the mediobasal hypothalamus (452).

Controversial data have been obtained regarding the involvement of endogenous HA in the regulation of ACTH and corticosteroid secretion.

In rats neither H_1 nor H_2 antagonists prevent the ACTH and corticosterone responses elicited by an acute restraint stress (678) and, in mice, neither His loads nor inhibition of HA synthesis by brocresine, a nonspecific decarboxylase inhibitor, modifies the corticosterone response to restraint (789). In contrast, histidine loading raises plasma corticosterone levels in rats (462). Specific inhibition of HDC by α-FMH decreases plasma corticosterone in nonstressed as well as in stressed rats; however, because this effect is not accompanied by any significant change in plasma ACTH, a direct action of the inhibitor at the adrenal level was suggested (678).

In contrast, in humans the H_1 antagonist meclastine prevents the ACTH response to hypoglycemia or metyrapone, a corticosteroid synthesis inhibitor (9). In addition, in rats treated with α-FMH the ACTH response to adrenalectomy is completely abolished (793).

F. Gonadotropin Secretion

Secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are under the control of gonadotropin-releasing hormone (GnRH), and the secretion of both the pituitary and hypothalamic hormones is modulated by gonadal steroids.

Intracerebroventricular administration of HA in large doses evokes ovulation in anesthetized rabbits (644) and LH release in ovariectomized rats primed with estrogen and progesterone (176, 184, 435) but not in male rats (181). This effect does not result from a direct stimulation at the pituitary level, since, in vitro, HA does not affect LH release from rat pituitary isolated cells (72) or fragments (123, 470). On the other hand, HA elicited GnRH release from perfused rat mediobasal hypothalamus, and GnRH was able to stimulate LH release from pituitaries sequentially perfused in a second perfusion chamber (470). The effect of HA could be mediated by H_1 receptors, since it was mimicked by 2-methylhistamine but not by 4-methylhistamine, two relatively selective agonists at H_1 and H_2 receptors, respectively, and antagonized by mepyramine, with the latter used, however, in high concentration (10 μM). Although not directly assessed, a possible involvement of endogenous HA in the control of LH release is suggested by the observation that castration increases HA level in the hypothalamus of male rats (529) and HDC activity in the hypothalamus of female rabbits (76) and that brain HA levels fluctuate in the hamster during the estrus cycle and on selected days of pregnancy (315).

VII. ROLE OF HISTAMINERGIC NEURONS IN CARDIOVASCULAR REGULATION

In conscious or anesthetized animals, i.e., rats, cats, or goats, intracerebroventricular administration of HA increases blood pressure accompanied by bradycardia in conscious animals or tachycardia in anesthetized animals (162, 214-216, 241, 396, 397, 453, 581, 691, 761, 775, 819). These effects are not attributable to leakage of HA into the general circulation, because the amine has an hypotensive action when administered peripherally.

The central hypertensive action of HA results only partially from an activation of sympathetic activity, a participation of endogenous vasopressin being suggested by the attenuation of the response observed with a vasopressin antagonist (241). Cerebral catecholaminergic pathways may also contribute to this action, which is reduced after intracerebroventricular administration of the neurotoxin 6-hydrodopamine (214). The hypertensive response to HA might involve both H_1 and H_2 receptors, as suggested by the action of various agonists, including the highly selective agonist impromidine, but the effects of antagonists, often used intracerebroventricularly in extremely large doses, has led to contradictory results (214-216, 303, 453, 538, 581). In contrast to the above effects, HA administered into the C_1 area of the rostral ventrolateral medulla causes hypotension and bradycardia selectively via stimulation of H_2 receptors (253). In cats, HA perfused at high concentration enhances the pressor effect of stimulation of the caudal hypothalamus selectively via H_2 receptors (562).

Endogenous HA might have a role in central cardiovascular regulation. The spontaneous release of HA in superfusates of cat posterior hypothalamus seems to be altered according to modifications of blood pressure (560, 561). In two studies (138, 582), spontaneously hypertensive rats displayed increased HA levels in several hypothalamic areas, e.g., suprachiasmatic or arcuate nucleus and median eminence, but not in various brain

stem areas, whereas others failed to detect any difference (118, 740). In these hypertensive rats, the rate of basal HA release in superfusates of the posterior hypothalamus is significantly increased (779). Elevated brain HA levels induced by an inhibitor of HMT were accompanied by increased blood pressure and bradycardia, but blockade of this response by HA antagonists was not reported (396). In fact, the effects of HA antagonists given alone do not clarify the issue of a possible role of endogenous HA. Whereas most H_1 antagonists crossing the blood-brain barrier display little cardiovascular activity (188), H_2 antagonists administered intracerebroventricularly elicit biphasic or even hypertensive effects similar to HA itself (215, 242, 397). This paradoxical effect might be related to blockade of either brain stem H_2 receptors mediating hypotensive actions (253) or H_2 autoreceptors controlling HA release for which several H_2 antagonists display significant affinity (25).

VIII. ROLE OF HISTAMINERGIC NEURONS IN CONTROL OF CEREBRAL CIRCULATION

A possible role of HA in the control of cerebral circulation is suggested by the presence of mast cells (see sect. IIIA) as well as of HA axons in vicinity of cerebral blood vessels (710). In addition, cerebral microvessels isolated by a sieving procedure contain measurable amounts of HA associated with HDC activity at a very low level (362, 381, 382) as well as H_1 receptors detected by [^{3}H]mepyramine binding (557) and H_2 receptors mediating a cAMP response (38, 381, 382).

Histamine has multiple actions on cerebral blood vessels (for review see Refs. 262, 263, 534, 535).

On pial arteries and arterioles, perivascular microinjection of the amine elicits dilation mainly via activation of H_2 receptors, whereas pial veins and venules seem unresponsive (200, 264, 266, 794). The HA-induced dilation of pial arterioles of newborn pigs seems to be due to a production of vasodilator prostanoids (469).

On precontracted isolated preparations of cat (200, 201, 264) or rabbit middle cerebral arteries (680), HA produces vasodilation apparently mediated by H_2 receptors. This response seems to involve the endothelium, and at higher concentrations vasoconstriction mediated by H_1 receptors is observed. On precontracted human cerebral arteries, dilation involves H_1 and, to a lesser extent, H_2 receptors (532). In the rabbit precontracted preparation in which H_1 and H_2 receptors were blocked, HA in low concentrations still elicited vasodilation via activation of H_3 receptors, and this effect is mimicked by the selective H_3 agonist α-MeHA in extremely low concentration (197). In rats, extraluminally administered HA causes dilation of the spontaneous tone of isolated intracerebral arterioles via activation of H_2 receptors (150).

Intracarotid injection of HA in rats increases cerebral blood flow via activation of both H_1 and H_2 receptors but only after transient disruption of the blood-brain barrier by hypertonic urea (261, 265, 267). This may reflect the fact that the cerebral vessels are more responsive to the amine when the latter is delivered to their external layers (534). In the human brain, however, transient vasodilative responses are observed, even when the blood-brain barrier is intact (750).

Histamine infused into rat internal carotid artery increases, via H_2-receptor stimulation, the extravascular space for sucrose or horseradish peroxidase as well as the cerebral water content; electron-microscopic studies showed pericapillary astroglial processes to be swollen, consistent with cerebral edema (84, 196, 267). Blockade of H_2 receptors by ranitidine partially prevented the kainic acid-induced formation of brain edema, which preferentially occurs in the thalamus (728). In contrast, blockade of H_1 receptors by mepyramine in reasonable dosage did not modify significantly regional cerebral glucose utilization in conscious rats (267).

IX. ROLE OF HISTAMINERGIC NEURONS IN THERMOREGULATION

Several data suggest that HA participates in central temperature regulation. A dose-related hypothermia is observed after either intracerebroventricular injection of the amine (130, 684) or its local application to the rostral hypothalamus (91), a site where some thermoresponsive neurons are also depressed by iontophoretic application of HA (726). The effect of intracerebroventricular HA is potentiated by pretreatment with amodiaquin, an inhibitor of HA methylation (141). *tele*-Methylhistamine, the main HA catabolite in brain, is ineffective when given intracerebroventricularly (141, 441). Loading mice with His in doses able to double brain HA level has no effect on temperature (140), but a similar treatment induces a fall in core temperature of rats (260), and this response is suppressed by blockade of HA synthesis (144). Burimamide, metiamide, or cimetidine, when centrally administered, antagonizes the hypothermia induced by His, 4-methylhistamine, dimaprit, or impromidine (143, 260, 515, 566). These data strongly suggest that H_2 receptors in brain mediate the hypothermic action of HA.

On the other hand, the hypothermia produced by the local application of HA into the hypothalamus was also prevented by a systemic injection of an H_1-receptor antagonist (91). Biphasic changes in the body temperature have been reported in cats after intracerebroventricular administration of HA (130). The immediate fall in temperature is followed by a slight hyperthermia occurring over a number of hours after the injection. Whereas mepyramine, a H_1 antagonist, blocks the HA-induced hypothermia, the delayed hyperthermia, which is mimicked by 4-methylhistamine, is suppressed by pretreatment with metiamide (130). To reconcile these findings it has been suggested (145) that HA affects the central thermoregulatory pathways by at least two mechanisms: stimulation of H_1 receptors located in the rostral hypothalamic thermoregulatory centers may lower the thermoregulatory set point, and stimulation of H_2 receptors, located elsewhere, may somehow activate efferent heat loss pathways directly.

The involvement of histaminergic systems in the thermal response to phencyclidine has also been proposed more recently (358). However, in anesthetized rats, stimulation of H_2 receptors in the nucleus preopticus medialis elicits a rise in core temperature (137).

Ionizing radiations in guinea pigs induce hypothermia, an effect mediated by both H_1 and H_2 receptors (376). Inhibition of HA synthesis by α-FMH did not modify body temperature in rats (33).

X. ROLE OF HISTAMINERGIC NEURONS IN EMESIS AND MOTION SICKNESS

Emesis is observed in dogs receiving HA intracerebroventricularly in high dosages, and the response is prevented by surgical ablation of the chemoreceptor trigger zone or by administration of H_1- and H_2-receptor antagonists (69, 70). The area postrema contains rather high levels of HDC activity in humans (657) and H_1 receptors in rodents (86, 414, 543).

Several H_1 antagonists are currently used to prevent motion sickness in humans, but their efficacy may derive from an associated antimuscarinic activity (188). Nevertheless, a possible role of endogenous HA is suggested by the presence of HA terminals and H_1 receptors in brain stem nuclei, such as the nucleus of the solitary tract or vestibular nuclei (7, 86) known to be involved in motion sickness.

On a behavioral model of motion sickness in rats, i.e., kaolin intake elicited by rotation, α-FMH had a beneficial effect; in addition, rotation induced a rise in brain stem HA that was prevented by labyrinthectomy (736).

XI. ROLE OF HISTAMINERGIC NEURONS IN CONTROL OF NOCICEPTIVE RESPONSES

A possible role of histaminergic neurons in the CNS in the control of pain has been recently reviewed (328, 626, 627).

Histamine administered intracerebroventricularly in rats (249) or mice (128, 526) impairs several nociceptive responses, e.g., in the writhing or hot plate jump tests, apparently via activation of H_2 receptors. A similar response is also observed after injections of HA onto neurons of the dorsal raphe (249) that are depressed (428); however, in contrast, this response apparently involves H_2 receptors. A control of pain perception by HA neurons would be consistent with their projections to and the presence of H_1 (86) and H_2 receptors (624a; M. L. Bouthenet, J. C. Schwartz, and M. Ruat, unpublished observations) in areas, e.g., the external of layers of the dorsal horn of the spinal cord and mesencephalic periventricular grey matter, known to be involved in nociceptive controls (67). However, the numerous studies on the effects on H_1-receptor antagonists administered alone do not clarify this issue (627). Several (but not all) compounds of this class display, like HA itself, antinociceptive activity in some tests involving supraspinal loci, whereas they are consistently ineffective in the tail flick response considered to be mainly controlled at the spinal level. In addition, many of these compounds block not only H_1 receptors but also muscarinic or serotoninergic receptors and the monoamine uptake systems. The fact that both the H_2 agonists and antagonists in high dosages (intracerebroventricularly) elicit antinociceptive responses does not clarify the issue. Thioperamide, a H_3 antagonist, does not modify a variety of nociceptive responses in mice (J. Costentin, personal communication).

A role of brain HA in a form of stress-induced antinociception has been postulated from the inhibition produced by the HDC inhibitor α-FMH or the H_1-antagonist diphenhydramine, whereas cimetidine was ineffective (434). However, others found cimetidine and other H_2 antagonists including zolantidine, a brain-penetrating compound, effective, whereas the H_1 antagonist chlorpheniramine was not (250, 328, 331).

Morphine does not affect HA or *t*-MeHA levels (340, 504) but increases HA turnover in mouse brain (504). However, a role of brain HA in morphine analgesia was not substantiated by the effects of receptor antagonists and a HDC inhibitor (340).

XII. ROLE OF HISTAMINERGIC NEURONS IN CONTROL OF VIGILANCE, SLEEP, AND WAKEFULNESS

A large body of experimental evidence now supports the hypothesis (577, 655) that histaminergic neuronal systems in mammalian brain play an important role in arousal.

Intracerebroventricular administration of HA causes electroencephalogram desynchronization in rabbits, and this action is antagonized by mepyramine (471, 824). Intracerebroventricular administration of 2-thiazolylethylamine, a relatively specific H_1 agonist but not that of dimaprit, a H_2 agonist, increases wakefulness at the expense of slow wave and paradoxical sleep in rats (polygraphic recordings), and this effect is antagonized by systemic mepyramine in low dosage (472). Histamine injected into the ventrolateral posterior hypothalamus elicits a similar effect in cats, which is also antagonized by mepyramine administered locally or systemically in low dosage (436, 437). In this last study it was verified that sodium nitrite, a potent vasodilator, has no similar effect, suggesting that the action of HA is not indirectly due to its local vascular effects. These clear-cut data indicate that stimulation of H_1 receptors in this area where they were visualized by autoradiography (86) mediates arousal in various mammalians. Because H_1 receptors do not appear to control either HA synthesis and release in vitro (25, 28) or the activity of histaminergic neurons in vivo (239, 570) and because short HA axons were visualized in this area (7), it appears that this arousal results from stimulation of postsynaptic H_1 receptors.

Various experimental approaches have also consistently shown that histaminergic neurons are involved in arousal mechanisms. In cats inhibition of HA synthesis by intraperitoneal α-FMH significantly increases deep slow-wave sleep and decreases wakefulness without modifying light slow-wave sleep and paradoxical sleep;

the drug has a similar effect when injected into the ventrolateral posterior hypothalamus (436, 437). The inhibitor administered systemically to rats has essentially similar effects; however, although in one study it was shown to occur during the "dark" phase (395, 793), in another study it mainly occurred during the "light" phase (473).

Conversely, inhibition of HA degradation via local injection of a HMT inhibitor to the ventrolateral posterior hypothalamus selectively increases wakefulness in cats (436, 437).

Arousal is also observed in cats after systemic administration of thioperamide, a H_3 antagonist, and to be blocked by administration of either *R*-α-MeHA, a H_3 agonist, or mepyramine, a H_1-receptor antagonist (437a). These effects suggest that modulation of endogenous HA release, via presynaptic H_3 receptors, indirectly affects arousal mechanisms controlled by postsynaptic H_1 receptors.

The effects observed after blockade of cerebral H_1 receptors by various antagonists administered alone also support the idea that endogenous HA is critically involved in the control of wakefulness. Systemic administration of mepyramine, one of the most selective H_1 antagonists, in low dosage (1–5 mg/kg) causes a significant dose-dependent increase in slow-wave sleep at the expense of wakefulness and paradoxical sleep in rats (472), dogs (808, 809), and cats (437). A similar effect is also observed in rats treated with diphenhydramine (394). In humans, mepyramine was recently shown not to affect the number of awakenings during sleep or the total sleep time (498). However, there is an abundant literature showing that many H_1 antagonists administered to humans during the day produce marked drowsiness, increase the tendency to sleep, decrease the sleep latency, and impair various performances (188, 208, 497). These various properties are designated together under the name of sedative properties that most H_1 antagonists share. All these compounds have the ability to occupy cerebral H_1 receptors at low dosages, i.e., in the therapeutic range or below, as judged from the [^{3}H]mepyramine binding test in the living mouse (589, 591). In contrast a number of recently designed compounds, which do not easily occupy cerebral H_1 receptors, as indicated by either the in vivo [^{3}H]mepyramine binding test or the direct measurement of their cerebral level, do not share these sedative properties and are therefore increasingly used in the therapy of allergic diseases (195, 497, 589, 591). Interestingly a variety of psychotropic agents, currently used in therapeutics as either antipsychotics or antidepressants, which display strong affinity for H_1 receptors in vitro (3, 287, 288, 610, 611, 757) and occupy cerebral H_1 receptors when administered at low dosage (589, 591), do share these characteristic sedative properties. Starting from these various observations it was proposed that sedation elicited by these various drugs in humans could be ascribed to blockade of the arousal mechanisms mediated by histaminergic neurons in brain (589, 591, 611, 655, 662). It has been argued that sedation may as well be ascribed to other properties of these compounds, i.e., to their ability to block muscarinic and α_1-adrenergic receptors, or to their local anesthetic activity (334, 696, 753, 780). However, in most cases, the affinity of these drugs for these other targets is much lower than for H_1 receptors so that only the latter are likely to be occupied in brain at low therapeutic dosage: for instance the K_i of mepyramine for H_1 receptors is at least 1,000-fold lower than for muscarinic receptors (420). In addition, the high potency toward H_1 receptors is the sole common property of these various sedative compounds.

The critical role of histaminergic neurons in arousal mechanisms is not only supported by pharmacological studies but also by the observations that bilateral damage or experimental lesioning of the posterior hypothalamus is accompanied by a state of somnolence or hypersomnia in humans (791a), monkeys (597), rats (464, 488), and cats (484, 485, 727). Furthermore, lesions of the ventrolateral posterior hypothalamus induced in cats by the neurotoxin ibotenic acid specifically aimed at destroying HA perikarya were followed during the next days by large decreases in wakefulness at the benefit of paradoxical and then of slow-wave sleep; after 3 days the animals recovered their control level of sleep, suggesting the intervention of compensatory mechanisms (638).

Cortically projecting HA neurons of rat tuberomammillary nucleus share with other aminergic neurons believed to control states of sleep and wakefulness a number of electrophysiological properties evidenced by extracellular recordings (604). They are firing spontaneously, slowly (2.0 ± 1.5 Hz) and with a regular pattern; their action potentials are of long duration (2–6 ms), with a pattern suggesting the existence of an electrotonic delay between spontaneously generated initial segment and somatodendritic spikes; and corresponding axons display low conduction velocity (0.3–0.5 m/s) consistent with the ultrastructural observations that a large fractions of HA axons are unmyelinated.

Both neurochemical and electrophysiological studies indicate that the activity of histaminergic neurons is maximal during periods of wakefulness. In several rat and guinea pig brain areas, particularly the hypothalamus, the HA level shows a reliable circadian rhythm with the minimum in the dark phase, during which rodents are the more active (529, 660, 777, 793); although levels of His and HDC were not modified, synthesis of [^{3}H]HA in hypothalamic slices was significantly higher when rats were killed during the dark phase (660). Because decreased amine levels and increased synthesis rates are usually associated with enhanced neuronal activity, it was postulated that this was also the case for histaminergic neurons and that these observations were taken as supporting their role in arousal mechanisms (660).

In the freely moving cat, single-unit extracellular recordings in the ventrolateral posterior hypothalamus detected two populations of neurons, the activity of which was strictly related to cortical desynchronization (784). One of them, which displayed electrophysiological properties very similar to HA neurons recorded in the tuberomammillary nucleus of the anesthetized rat

(604), was highly selective for the waking state. During active wakening these neurons discharged slowly and regularly, the firing rate then became progressively slowed during "calm wakening" and, even more, light slow-wave sleep; these neurons were completely silent during deep slow-wave or paradoxical sleep (784). Barbiturates and other hypnotics dramatically decrease HA turnover in brain (327, 571).

Hence a variety of complementary experimental approaches indicate that HA neurons exert a major control in wakening mechanims, their best substantiated functional role so far. Available experimental evidence suggests that this action is mainly subserved via H_1 receptors, but the role of H_2 receptors remains to be thoroughly investigated. It has been underlined that the essentially modulatory mode of action of HA mediated by H_2 receptors at the cellular level and the anatomic disposition of HA pathways fit particularly well with a role in the regulation of states of awareness (276, 577). Finally, H_3 receptors may also participate by controlling not only the activity of HA neurons but also that of other neuronal systems.

XIII. ROLE OF HISTAMINERGIC NEURONS IN CONTROL OF VARIOUS BEHAVIORS

Relatively little research has been centered on the role of histaminergic systems in the control of complex behaviors (for review see Ref. 816).

A. Stress

Contradictory results have been reported regarding the effects of various stressful procedures in rats and mice.

In rats, forced immobilization and/or cold exposure decreased HA levels and increased HA turnover in hypothalamus (742, 744), but the effect on HA levels could not be confirmed by others (408). Air blasts increased HA levels and HDC activity in rats (461, 463).

In mice, forced immobilization for a relatively short period reduced whole brain HA turnover without affecting HA levels (789), whereas the same treatment for several hours decreased HA levels (745). Footshock stress for 30-120 min did not affect HA levels but enhanced HA turnover, an effect partly mediated by endogenous opioids (835).

B. Motor Activity

Intracerebroventricular administration of HA elicits biphasic changes in spontaneous locomotor activity in fowl (509), rats (373), and goats (774), with the hyperactivity response being, in all cases, mediated by H_1 receptors. However, in other studies only hypoactivity was observed (110, 525). Inhibition of locomotion, apparently mediated by H_1 and H_2 receptors, was observed in rats shortly after injection of HA into the ventral hippocampus (14). Intra-accumbens injection of HA in rats elicited an initial hypoactivity, apparently mediated by H_2 receptors, followed by hyperactivity, apparently mediated by H_1 receptors (93, 94).

In mice, histidine loads reduce the amphetamine-induced locomotor activity (142, 355), an effect that might involve endogenous HA, as it is suppressed by administration of α-FMH (355).

In humans, several H_1 antagonists known to cross the blood-brain barrier impair psychomotor performance evaluated in a variety of complex skilled tasks (for review see Ref. 816).

C. Drinking and Eating

A role for peripheral HA in the control of periprandial drinking has been proposed (415) but is not considered here. When injected into several hypothalamic areas, particularly the medial rostral areas, HA elicits drinking in water-satiated rats and increases drinking in water-deprived rats (247, 430, 431). These effects appear to involve both H_1 and H_2 receptors, but blockade of these receptors by peripherally administered antagonists does not result in clear-cut effects on drinking behavior (415–417, 431).

When injected intracerebroventricularly, HA suppresses food intake in cats, an effect possibly mediated by H_1 receptors (133). However, in rats, when the amine is injected into the hypothalamus (136) or continuously infused into the suprachiasmatic nucleus (793), it has an opposite effect.

A possible role of endogenous HA in the control of food intake is suggested by the observation that H_1 but not H_2 antagonists induce feeding in rats when infused into the ventromedial hypothalamus during the light phase of the day; this effect was prevented by pretreatment with α-FMH (527a, 634, 635). Histidine loads (685) or thioperamide (T. K. Sakata, personal communication) suppress food intake.

D. Aggressive Behaviors

Intracerebroventricular administration of HA decreases electric shock-induced fighting in rats (450, 598) but has an opposite action when administered in high doses to mice (486). Histidine loads inhibit the same behavior in mice (142). Various H_1 antagonists, generally in high dosage, suppress isolation-induced fighting in mice (46) or muricide activity in rats (527).

E. Self-Stimulation, Reinforcement, and Aversion

Histamine injected into rat hypothalamic perifornical area, where an electrode for self-stimulation was implanted, inhibited self-stimulation, and the effect was blocked by H_1 antagonists (136). Mepyramine decreases self-stimulation, but chlorpheniramine has an opposite effect (807).

The H_1 antagonists are self-administered intravenously in squirrel monkeys (63) but not orally in rats (222).

When intracerebroventricular administration of HA was paired with administration of a sucrose solution, taste aversion to the later developed (596).

F. Learning

Intracerebroventricular administration of HA to rats improved the retention of a learned behavior, apparently via stimulation of both H_1 and H_2 receptors (161).

G. Discriminative Properties of H_1 Antagonists

In various animals trained to discriminate a H_1 antagonist from saline, there is complete generalization to most other drugs of this class (533, 815, 823). This suggests that the H_1 antagonists share some common behavioral properties but does not clarify the nature of the latter.

H. Hallucinatory Properties of H_2 Antagonists

There are several reports indicating that in a small number of patients taking cimetidine or ranitidine visual or auditory hallucinations may occur, perhaps as a result of altered blood-brain barrier permeability (for review see Ref. 816). It is not clear, however, whether these effects are selectively related to H_2 receptor blockade.

XIV. CONCLUSION

During the last few decades, many reviews on the physiological role of HA in the brain were almost uniformly concluded by the assertion that the amine should be considered as a putative neurotransmitter. The data reviewed here demonstrate, beyond any reasonable doubt, that this role is now fully established. Histaminergic neurons, although in small number, constitute one of these long tracts with widespread projections to large CNS areas, particularly in diencephalon and telencephalon. The localization of their target cells and the modes of action of HA at their level, as it is mediated by the three receptor subtypes, seems also largely, although incompletely, unraveled. From the available information it has been for a long time suspected that histaminergic neurons may coordinate diverse sensory, motor, hormonal, and vegetative functions to act in a concerted manner. These rather vague functions are similar to those currently ascribed to other aminergic neurons (noradrenergic, serotoninergic), but the picture is somewhat less clear in the case of HA. One of the major challenges to take up now seems to be the understanding of the exact functional role of histaminergic neurons. Their implication in a variety of biological and physiological processes (e.g., arousal, pituitary hormone secretion, control of cerebral circulation, thermoregulation) has been so far mainly suggested from the observed actions of HA or, in few cases, of agents modifying histaminergic transmissions in the brain. However, in most cases, one notable exception being arousal: there is a lack of evidence that these physiological activities are correlated with changes in neuronal histaminergic activity.

Monitoring these changes in behaving animals seems a prerequisite to more firmly confirm these various contentions. Establishing the nature of the information received by histaminergic neurons seems equally important in this respect. Also, as in the case of most other neuronal populations, the functional significance of coexisting neurotransmitters, which are particularly numerous in histaminergic neurons, needs to be established. In addition there is, so far, no clear indication regarding a possible implication of histaminergic neurons in pathophysiology.

Finally, a major challenge that remains to be taken up is the understanding of the functions of the nonneuronal store(s) of HA in the CNS.

The dramatic progress recorded during the last few years in understanding the other functions of the amine make us confident that little time will elapse before these remaining and exciting physiological problems are solved.

The skillful secretarial assistance of Annie Galtier and Mireille Castrières is gratefully acknowledged.

REFERENCES

1. ABEL, J. J., AND S. KUBOTA. Presence of histamine (4-imidazoleethylamine) in the hypophysis cerebri and other tissues of the body and its occurrence among the hydrolytic decomposition products of proteins. *J. Pharmacol.* 12: 243, 1919.
2. ABOU, Y. Z., H. M. ADAM, AND W. R. G. STEPHEN. Concentration of histamine in different parts of the brain and hypophysis of rabbit: effect of treatment with histidine, certain other amino acids and histamine. *Br. J. Pharmacol.* 48: 577–589, 1973.
3. ACEVES, J., S. MARISCAL, K. E. MORRISON, AND J. M. YOUNG. The binding of doxepin to histamine H_1 receptors in guinea pig and rat brain. *Br. J. Pharmacol.* 84: 417–424, 1985.
4. ADAM, H. M. Histamine in the central nervous system and hypophysis of the dog. In: *Regional Neurochemistry*, edited by S. S. Kety and J. Elkes. Oxford, UK: Pergamon, 1961, p. 293–306.
5. ADAM, H. M., AND H. K. A. HYE. Concentration of histamine in different parts of the brain and hypophysis of the cat and its modifications by drugs. *Br. J. Pharmacol.* 28: 137–152, 1966.
6. AHN, H. S., AND A. BARNETT. Selective displacement of [^{3}H]mepyramine from peripheral vs. central nervous system receptors by loratadine, a non-sedating antihistamine. *Eur. J. Pharmacol.* 127: 153–155, 1986.

6a. AIRAKSINEN, M. S., G. FLUGGE, E. FUCHS, AND P. PANULA. Histaminergic system in the tree shrew brain. *J. Comp. Neurol.* 286: 289–310, 1990.

7. AIRAKSINEN, M. S., AND P. PANULA. The histaminergic system in the guinea-pig central nervous system: an immunocytochemical mapping using an antiserum against histamine. *J. Comp. Neurol.* 273: 163–186, 1988.

7a. AIRAKSINEN, M. S., AND P. PANULA. Comparative neuroanatomy of the histaminergic system in the brain of the frog *Xenopus laevis*. *J. Comp. Neurol.* 292: 412–423, 1990.

8. AL-GADI, M., AND S. J. HILL. Characterization of histamine receptors mediating the stimulation of cyclic AMP accumulation in rabbit cerebral cortical slices. *Br. J. Pharmacol.* 85: 877–888, 1985.
9. ALLOLIO, B, U. DEUSS, D. KAULEN, AND W. WINKELMANN. Effect of meclastine, a selective H_1 receptor antagonist upon ACTH release. *Clin. Endocrinol.* 19: 239–245, 1983.
10. ALMEIDA, A. P., AND M. A. BEAVEN. Phylogeny of histamine in vertebrate brain. *Brain Res.* 208: 244–250, 1981.
11. ALOE, L., AND R. LEVI-MONTALCINI. Mast cells increase in tissues of neonatal rats injected with the nerve growth factor. *Brain Res.* 133: 358–366, 1977.
12. ALVAREZ, E. O. Role of histamine in the increased secretion of prolactin induced by ether in the adult male rat. *J. Endocrinol. Metab.* 56: 409–416, 1982.
13. ALVAREZ, E. O. Induction of prolactin release by H_1- or H_2-histamine agonists in maturing male and female rats. *J. Neural Transm.* 59: 241–250, 1984.
14. ALVAREZ, E. O., AND A. M. BANZAN. Further evidence that histamine in hippocampus affects the exploratory behavior in the rat. *Physiol. Behav.* 34: 661–664, 1985.
15. ALVAREZ, E. O., AND A. O. DONOSO. Effects of histamine implants in several brain regions on the release of prolactin in conscious adult male rats. *J. Endocrinol.* 88: 351–358, 1981.
16. ANDO-YAMAMOTO, M., H. HAYASHI, Y. TAGUCHI, H. FUKUI, T. WATANABE, AND H. WADA. Demonstration of immunohistochemical and immunochemical cross-reactivity of L-histidine and L-DOPA decarboxylases using antibodies against the two enzymes. *Biochem. Biophys. Res. Commun.* 141: 306–312, 1986.
17. ANDO-YAMAMOTO, M., H. KIYAMA, H. HAYASHI, H. FUKUI, M. TOHYAMA, T. WATANABE, AND H. WADA. Demonstration of histaminergic neurons in horizontal cells of guinea-pig retina. *Brain Res.* 410: 269–274, 1987.
18. ARAKELIAN, M. C., AND C. LIBERTUN. H_1 and H_2 histamine receptor participation in the brain control of prolactin secretion in lactating rats. *Endocrinology* 100: 890–895, 1977.
19. ARMSTRONG, W. E., AND C. D. SLADEK. Evidence for excitatory actions of histamine on supraoptic neurons in vitro: mediation by an H_1-type receptor. *Neuroscience* 16: 307–322, 1985.
20. ARNOULD, J. M. Mise en évidence de la carcinine synthétase, une nouvelle enzyme catalysant le métabolisme de l'histamine dans le système nerveux central de *Carcinus maenas*. *J. Neurochem.* 48: 1316–1324, 1987.
21. ARRANG, J. M., N. DEFONTAINE, AND J. C. SCHWARTZ. Phencyclidine blocks histamine H_3-receptors in rat brain. *Eur. J. Pharmacol.* 157: 31–35, 1988.
22. ARRANG, J. M., B. DEVAUX, J. P. CHODKIEWICZ, AND J. C. SCHWARTZ. H_3-receptors control histamine release in human brain. *J. Neurochem.* 51: 105–108, 1988.
23. ARRANG, J. M., M. GARBARG, J. C. LANCELOT, J. M. LECOMTE, H. POLLARD, M. ROBBA, W. SCHUNACK, AND J. C. SCHWARTZ. Highly potent and selective ligands for histamine H_3-receptors. *Nature Lond.* 327: 117–123, 1987.
24. ARRANG, J. M., M. GARBARG, T. T. QUACH, M. DAM TRUNG TUONG, E. VERLAMIAN, AND J. C. SCHWARTZ. Actions of betahistine at histamine receptors in the brain. *Eur. J. Pharmacol.* 111: 73–84, 1985.
25. ARRANG, J. M., M. GARBARG, AND J. C. SCHWARTZ. Autoinhibition of brain histamine release mediated by a novel class (H_3) of histamine receptor. *Nature Lond.* 302: 832–837, 1983.
26. ARRANG, J. M., M. GARBARG, AND J. C. SCHWARTZ. Histamine synthesis and release in CNS: control by autoreceptors (H_3). In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 143–153.
27. ARRANG, J. M., M. GARBARG, AND J. C. SCHWARTZ. Autoregulation of histamine release in brain by presynaptic H_3-receptors. *Neuroscience* 15: 553–562, 1985.
28. ARRANG, J. M., M. GARBARG, AND J.,C. SCHWARTZ. Autoinhibition of histamine synthesis mediated by presynaptic H_3-receptors. *Neuroscience* 23: 149–157, 1987.

28a. ARRANG, J. M., J. ROY, J. L. MORGAT, W. SCHUNACK, AND J. C. SCHWARTZ. Histamine H_3-receptor binding sites in rat brain membranes: modulation by guanine nucleotides and divalent cations. *Eur. J. Pharmacol.* 188: 219–227, 1990.

29. ARRANG, J. M., J. C. SCHWARTZ, AND W. SCHUNACK. Stereoselectivity of the histamine H_3-presynaptic autoreceptor. *Eur. J. Pharmacol.* 117: 109–114, 1985.
30. ASANO, Y., R. W. WOODWARD, D. R. HOUCK, AND H. G. FLOSS. Stereochemical course of the transmethylation catalyzed by histamine *N*-methyltransferase. *Arch. Biochem. Biophys.* 231: 253–256, 1984.
31. ASH, A. S. F., AND H. O. SCHILD. Receptors mediating some actions of histamine. *Br. J. Pharmacol. Chemother.* 27: 427–439, 1966.
32. ATACK, C., AND A. CARLSSON. In vitro release of endogenous histamine, together with noradrenaline and 5-hydroxytryptamine, from slices of mouse cerebral hemispheres. *J. Pharm. Pharmacol.* 24: 990–992, 1972.
33. AURES, D., R. HÅKANSON, AND W. G. CLARK. Histidine decarboxylase and dopa decarboxylase. In: *Handbook of Neurochemistry. Control Mechanisms in the Nervous System*, edited by A. Lajtha. New York: Plenum, 1970, vol. 4, p. 165–187.
34. AUTIO, V., AND P. ERMALA. Determination of histamine in cerebrospinal fluid in some neuropsychiatric cases. *Ann. Med. Exp. Biol. Fenn.* 27: 87–91, 1949.
35. AUVINEN, S., AND P. PANULA. Development of histamine-immunoreactive neurons in the rat brain. *J. Comp. Neurol.* 276: 289–303, 1988.
36. AXELROD, J., P. D. MACLEAN, R. ALBERS WAYNE, AND H. WEISSBACH. Regional distribution of methyltransferase enzymes in the nervous system and glandular tissues. In: *Regional Neurochemistry: Proceedings*, edited by S. S. Kety and J. Elkes. London: Pergamon, 1961, p. 307–311. (Int. Neurochem. Symp., 4th)
37. BABA, M., M. NISHIBORI, R. OISHI, K. SAEKI, AND F. KOSAKA. Effects of halothane, enflurane and pentobarbital on brain histamine dynamics in mice. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 335: 686–691, 1987.
38. BACA, G. M., AND G. C. PALMER. Presence of hormonally-sensitive adenylate cyclase receptors in capillary-enriched fractions from rat cerebral cortex. *Blood Vessels* 15: 286–298, 1978.
39. BARABAN, J. M., S. H. SNYDER, AND B. E. ALGER. Protein kinase C regulates ionic conductance in hippocampal pyramidal neurons: electrophysiological effects of phorbol esters. *Proc. Natl. Acad. Sci. USA* 82: 2538–2542, 1985.
40. BARBIN, G., M. GARBARG, J. C. SCHWARTZ, AND J. STORM-MATHISEN. Histamine synthesizing afferents to the hippocampal region. *J. Neurochem.* 26: 259–265, 1976.
41. BARBIN, G., J. C. HIRSCH, M. GARBARG, AND J. C. SCHWARTZ. Decrease in histamine content and decarboxylase activities in an isolated area of the cerebral cortex of the cat. *Brain Res.* 92: 170–174, 1975.
42. BARBIN, G., J. M. PALACIOS, M. GARBARG, J. C. SCHWARTZ, P. GASPAR, F. JAVOY-AGID, AND Y. AGID. L-Histidine decarboxylase in the human brain: properties and localization. *J. Neurochem.* 35: 400–406, 1980.
43. BARBIN, G., J. M. PALACIOS, E. RODERGAS, J. C. SCHWARTZ, AND M. GARBARG. Characterization of the high-affinity binding sites of [^{3}H]-histamine in rat brain. *Mol. Pharmacol.* 18: 1–10, 1980.
44. BARGER, G., AND H. H. DALE. 4-β-Aminoethylglyoxaline (β-iminazolylethylamine) and the other active principles of ergot. *J. Chem. Soc.* 97: 2592–2595, 1910.
45. BARKER, J. L., J. W. CRAYTON, AND R. A. NICOLL. Noradrenaline and acetylcholine responses of supraoptic neurosecretory cells. *J. Physiol. Lond.* 218: 19–32, 1971.
46. BARNETT, A., J. B. MALICK, AND R. I. TABER. Effects of antihistamines on isolation-induced fighting in mice. *Psychopharmacologia* 19: 359–365, 1971.
47. BARTH, H., W. LORENZ, AND I. NIEMEYER. Inhibition and activation of histamine methyltransferase by methylated histamines. *Hoppe Seyler's Z. Physiol. Chem.* 354: 1021–1026, 1973.
48. BATESON, M. C., M. C. K. BROWNING, AND A. MACONNACHIE. Galactorrhoea with cimetidine. *Lancet* 2: 247–248, 1977.
49. BATZRI, S., AND J. W. HARMON. Is [^{3}H]-tiotidine a specific ligand for the H_2-receptor? *Pharmacology* 32: 241–247, 1986.

50. BATZRI, S., J. W. HARMON, J. DYER, AND W. F. THOMPSON. Interaction of histamine with gastric mucosal cells. Effect of histamine H_2 antagonists on binding and biological response. *Mol. Pharmacol.* 22: 41–47, 1982.
51. BATZRI, S., J. W. HARMON, AND W. F. THOMPSON. Interaction of histamine with gastric mucosal cells. Effect of histamine agonists on binding and biological response. *Mol. Pharmacol.* 22: 33–40, 1982.
52. BATZRI, S., J. W. HARMON, AND M. D. WALKER. Identification of [^{3}H]-histamine binding sites on gastric mucosal cells unrelated to histamine H_2-receptors. *Biochem. Biophys. Res. Commun.* 108: 965–969, 1982.
53. BAUDRY, M., P. CHAST, AND J. C. SCHWARTZ. Studies on *S*-adenosylhomocysteine inhibition of histamine transmethylation in brain. *J. Neurochem.* 20: 13–21, 1973.
54. BAUDRY, M., J. EVANS, AND G. LYNCH. Excitatory amino acids inhibit stimulation of phosphatidylinositol metabolism by aminergic agonists in hippocampus. *Nature Lond.* 319: 329–331, 1986.
55. BAUDRY, M., M. P. MARTRES, AND J. C. SCHWARTZ. The subcellular localisation of histidine decarboxylase in various regions of rat brain. *J. Neurochem.* 21: 1301–1309, 1973.
56. BAUDRY, M., M. P. MARTRES, AND J. C. SCHWARTZ. H_1 and H_2 receptors in the histamine-induced accumulation of cyclic AMP in guinea pig brain slices. *Nature Lond.* 253: 362–363, 1975.
57. BEAUDET, A., AND L. DESCARRIES. The monoamine innervation of rat cerebral cortex: synaptic and nonsynaptic axon terminals. *Neuroscience* 3: 851–860, 1978.
58. BEAVEN, M. A., AND R. E. SHAFF. New inhibitors of histamine-*N*-methyltransferase. *Biochem. Pharmacol.* 28; 183–188, 1979.
59. BENARDO, L. S., AND D. A. PRINCE. Ionic mechanisms of cholinergic excitation in mammalian hippocampal pyramidal cells. *Brain Res.* 249: 333–344, 1982.
60. BEN-ARI, Y., G. LE GAL LA SALLE, G. BARBIN, J. C. SCHWARTZ, AND M. GARBARG. Histamine synthesizing afferents within the amygdaloid complex and bed nucleus of the stria terminalis of the rat. *Brain Res.* 138: 285–294, 1977.
61. BENNETT, C. T., AND A. PERT. Antidiuresis produced by injections of histamine into the cat supraoptic nucleus. *Brain Res.* 78: 151–156, 1974.
62. BENNETT, G. W., AND M. KEELING. H_2-mediated histamine induced release of thyrotropin-releasing hormone (TRH) from hypothalamic synaptosomes: a neuroendocrine role for histamine. *Br. J. Pharmacol.* 72: 151–152, 1981.
63. BERGMAN, J., AND R. D. SPEALMAN. Some behavioural effects of histamine H_1 antagonists in squirrel monkeys. *J. Pharmacol. Exp. Ther.* 239: 104–110, 1986.
64. BERKENBOSH, F., AND H. W. STEINBUSCH. Histamine-immunostaining in the rat median eminence: an unexpected form of cross-reactivity with LH-RH. *Brain Res.* 405: 353–357, 1987.
65. BERRIDGE, M. J., C. P. DOWNES, AND M. R. HANLEY. Lithium amplifies agonist-dependent phosphatidylinositol responses in brain and salivary glands. *Biochem. J.* 206: 587–595, 1982.
66. BERRIDGE, M. J., AND R. F. IRVINE. Inositol triphosphate, a novel second messenger in cellular signal transduction. *Nature Lond.* 312: 315–321, 1984.
67. BESSON, J. M., AND A. CHAOUCH. Peripheral and spinal mechanisms of nociception. *Physiol. Rev.* 67: 67–186, 1987.
68. BEST, C. G., H. H. DALE, H. W. DUDLEY, AND W. V. THORPE. The nature of the vaso-dilator constituents of certain tissue extracts. *J. Physiol. Lond.* 62: 397–417, 1927.
69. BHARGHAVA, K. P. Some neuropharmacological studies with histamine. In: *Neuropsychopharmacology*, edited by J. R. Boissier, H. Hippius, and P. Pichot. Amsterdam: Excerpta Med., 1975, p. 597–604.
70. BHARGHAVA, K. P., K. S. DIXIT, AND G. PALIT. Nature of histamine receptors in the emetic chemoreceptor trigger zone. *Br. J. Pharmacol.* 57: 211–213, 1976.
71. BHARGHAVA, K. P., V. K. KULSHRESTA, G. SANTHAKUMRI, AND Y. P. SRIVASTAVA. Mechanism of histamine-induced antidiuretic response. *Br. J. Pharmacol.* 47: 700–706, 1973.
72. BICKNELL, R. J., AND B. K. POLLET. A quantitative assay for luteinizing hormone releasing hormone (LHRH) using dispersed pituitary cells. *Gen. Comp. Endocrinol.* 26: 141–152, 1975.
73. BIELKIEWICZ, B., AND D. A. COOK. Tha binding of [^{3}H] mepyramine to histamine H_1 receptors in monkey brain. *J. Physiol. Pharmacol.* 63: 756–759, 1985.
74. BIGGS, M. J., AND E. S. JOHNSON. Electrically-evoked release of [^{3}H]histamine from the guinea-pig hypothalamus. *Br. J. Pharmacol.* 70: 555–560, 1980.
75. BISCHOFF, S., AND J. KORF. Different localisation of histidine decarboxylase and histamine-*N*-methyltransferase in the rat brain. *Brain Res.* 141: 375–379, 1978.
76. BJORKLUND, A., R. HÅKANSON, A. NOBIN, AND N. O. SJÖBERG. Increase in rabbit hypothalamic histidine decarboxylase activity after cophorectomy and thyroidectomy. *Experientia Basel* 26: 1232–1233, 1972.
77. BLACK, J. W., W. A. M. DUNCAN, C. J. DURANT, C. R. GANELLIN, AND M. E. PARSONS. Definition and antagonism of histamine H_2-receptors. *Nature Lond.* 236: 385–390, 1972.
78. BLAKEMORE, R. C., C. R. GANELLIN, M. GARBARG, C. GROS, R. J. IFE, M. KÖRNER, M. RUAT, J. C. SCHWARTZ, W. TERTUK, AND C. J. THEOBALD. Iodobolpyramine and other iodinated derivatives as ligands for detecting histamine H_1 receptors. *Eur. J. Med. Chem.* 22: 91–100, 1987.
79. BLANCO, I., M. BLANCO, M. GRAU, J. M. PALACIOS, F. PICATOSTE, AND G. SCHERK. Distribution of histamine in 7 brain regions in different species and strains of mammals. *Experientia Basel* 29: 791–793, 1973.
79a. BLANDINA, P., P. J. KNOTT, L. K. H. LEUNG, AND J. P. GREEN. Stimulation of histamine H_2 receptor in rat hypothalamus releases endogenous norepinephrine. *J. Pharmacol. Exp. Ther.* 245: 44–51, 1989.
80. BLEIER, R., P. COHN, AND I.R. SIGGELCOW. A cytoarchitectonic atlas of the hypothalamus and hypothalamic third ventricle of the rat. In: *Handbook of the Hypothalamus. Anatomy of the Hypothalamus*, edited by P. J. Morgane and J. Panksepp. New York: Dekker, 1979, vol. 1, p. 127–220.
81. BORCHARDT, R. T., AND B. MATUSZEWSKA. *S*-adenosylmethionine-dependent transmethylation of histamine: purification and partial characterization of guinea pig brain and rat kidney histamine *N*-methyltransferase. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 163–172.
82. BOUCLIER, M., M. J. JUNG, AND F. GERHART. Effect of prolonged inhibition of histidine decarboxylase on tissue histamine concentrations. *Experientia Basel* 39: 1303–1305, 1983.
83. BOUCLIER, M., M. J. JUNG, AND F. GERHART. α-Fluoromethyl histidine. Inhibition of histidine decarboxylase in pylorus ligated rat. *Biochem. Pharmacol.* 32: 1553–1556, 1983.
84. BOURKE, R. S., H. K. KIMELBERG, L. R. NELSON, K. D. BARRON, E. L. AUEN, A. J. POPP, AND J. B. WALDMAN. Biology of glial swelling in experimental brain edema. In: *Brain Edema: Pathology, Diagnosis and Therapy*, edited by J. Cervos-Navarro and R. Ferstl. New York: Raven, 1980, p. 99–109. (Adv. Neurol. Ser., vol. 28)
85. BOUTHENET, M. L., M. P. MARTRES, N. SALES, AND J. C. SCHWARTZ. A detailed mapping of dopamine D-2 receptors in rat central nervous system by autoradiography with [^{125}I]iodosulpride. *Neuroscience* 20: 117–155, 1987.
86. BOUTHENET, M. L., M. RUAT, N. SALES, M. GARBARG, AND J. C. SCHWARTZ. A detailed mapping of histamine H_1-receptors in guinea-pig central nervous system established by autoradiography with [^{125}I]iodobolpyramine. *Neuroscience* 26: 553–600, 1988.
87. BOVET, D., AND A. M. STAUB. Action protectrice des éthers phénoliques au cours de l'intoxication histaminique. *C. R. Seances Soc. Biol. Paris* 124: 547–549, 1937.
88. BOWSHER, R. R., K. M. VERBURG, AND D. P. HENRY. Rat histamine *N*-methyltransferase. Quantification, tissue distribution, purification, and immunologic properties. *J. Biol. Chem.* 258: 12215–12220, 1983.
89. BRADLEY, P. B. Synaptic transmission in the CNS and its relevance for drug action. *Int. Rev. Neurobiol.* 11: 1–56, 1968.
90. BRADLEY, P. B., H. JONES, AND P. ROBERTS. Histamine potentiates the effects of excitatory aminoacids on quiescent neurones in the rat medulla (Abstract). *Br. J. Pharmacol.* 82: 195P, 1984.
91. BREZENOFF, H. E., AND P. LOMAX. Temperature changes fol-

lowing microinjection of histamine into the thermoregulatory centers of the rat. *Experientia Basel* 26: 51–53, 1970.
92. BRISTOW, D. R., J. R. HARE, J. R. HEARN, AND L. E. MARTIN. Radioligand binding studies using [^{3}H]-cimetidine and [^{3}H]-ranitidine (Abstract). *Br. J. Pharmacol.* 74: 547P, 1981.
93. BRISTOW, L. J., AND G. W. BENNETT. Biphasic effects of intracaudate histamine administration on spontaneous motor activity in the rat; a role for central histamine receptors. *Br. J. Pharmacol.* 95: 1292–1302, 1988.
94. BRISTOW, L. J., AND G. W. BENNETT. A role for histamine H_2 receptors in histamine-induced hypoactivity in the rat (Abstract). *Br. J. Pharmacol.* 94: 319P, 1988.
95. BROCH, O. J., AND F. FONNUM. The regional and subcellular distribution of C.O.M.T. in the rat brain. *J. Neurochem.* 19: 2049–2055, 1972.
96. BROWN, D. D., R. TOMCHICK, AND J. AXELROD. The distribution and properties of a histamine methylating enzyme. *J. Biol. Chem.* 234: 2948–2950, 1959.
97. BROWN, E., D. A. KENDALL, AND S. R. NAHORSKI. Inositol phospholipid hydrolysis in rat cerebral cortical slices. I. Receptor characterization. *J. Neurochem.* 42: 1379–1387, 1984.
98. BROWNSTEIN, M. J., J. M. SAAVEDRA, M. PALKOVITS, AND J. AXELROD. Histamine content of hypothalamic nuclei of the rat. *Brain Res.* 77: 151–156, 1974.
99. BUGAJSKI, J., AND A. GADEK. Central H_1- and H_2-histaminergic stimulation of pituitary-adrenocortical response under stress in rats. *Neuroendocrinology* 36: 424–430, 1983.
100. BUGAJSKI, J., AND A. GADEK. The effect of adrenergic and cholinergic antagonists on central histaminergic stimulation of pituitary-adrenocortical response under stress in rats. *Neuroendocrinology* 38: 447–452, 1984.
101. BUGAJSKI, J., AND Z. JANUSZ. Central histaminergic stimulation of pituitary-adrenocortical response in the rat. *Life Sci.* 33: 1179–1189, 1983.
102. BURKARD, W. P. Histamine H_2-receptor binding with [^{3}H]-cimetidine in brain. *Eur. J. Pharmacol.* 50: 449–450, 1978.
103. BURKARD, W. P., K. F. GEY, AND A. PLETSCHER. Diamine oxidase in the brain of vertebrates. *J. Neurochem.* 10: 183–186, 1963.
104. BURLAND, W. L., R. I. GLEADLE, R. M. LEE, D. ROWLEY-JONES, AND G. V. GROOM. Prolactin responses to cimetidine. *Br. J. Clin. Pharmacol.* 7: 19–21, 1979.
105. BUSCHAUER, A., W. SCHUNACK, J. M. ARRANG, M. GARBARG, J. C. SCHWARTZ, AND J. M. YOUNG. Histamine receptors. In: *Receptor Pharmacology and Function*, edited by M. Williams, R. A. Glennon, and P. B. M. W. M. Timmermans. New York: Dekker, 1989, p. 293–348.
106. CACABELOS, R., H. NIIGAWA, A. YAMATODANI, A. GOMEZ-PAN, T. NISHIMURA, AND H. WADA. Antagonist effects of growth hormone-releasing factor and somatostatin on brain histamine. *Endocrinology* 122: 1269–1276, 1988.
107. CACABELOS, R., A. YAMATODANI, H. NIIGAWA, S. HARIGUCHI, T. NISHIMURA, AND H. WADA. Histaminergic neuromodulation of the release of vasopressin. *Neuroendocrinology* 45: 368–375, 1987.
108. CALCUTT, C. R., C. R. GANELLIN, R. GRIFFITHS, B. K. LEIGH, J. P. MAGUIRE, R. C. MITCHELL, M. E. MYLEK, M. E. PARSONS, I. R. SMITH, AND R. C. YOUNG. Zolantidine (SK&F 96282) is a potent selective brain penetrating histamine H_2-receptor antagonist. *Br. J. Pharmacol.* 93: 69–78, 1988.
109. CALCUTT, C. R., C. R. GANELLIN, B. JACKSON, B. K. LEIGH, D. A. A. OWEN, AND I. R. SMITH. Evidence for low brain penetration by the H_1-receptor antagonist temelastine (SK F 93944). *Eur. J. Pharmacol.* 133: 65–74, 1987.
110. CALCUTT, C. R., AND J. REYNOLDS. Some behavioural effects following intracerebroventricular (i.c.v.) injection in rats of histamine H_1 and H_2-receptor agonists and antagonists. *Neurosci. Lett.* 3: 82–83, 1976.
111. CAMMERMEYER, J. Mast cells in the mammalian area postrema. *Z. Anat. Entwicklungsgesch.* 139: 71–92, 1972.
112. CARETTE, B. Responses of preoptic septal neurons to iontophoretically applied histamine. *Brain Res.* 145: 391–395, 1978.
113. CARLINI, E. A., AND J. P. GREEN. The subcellular distribution of histamine, slow reacting substance and 5-hydroxytryptamine in the brain of the rat. *Br. J. Pharmacol.* 20: 264–277, 1963.
114. CARLSON, H. E., AND A. F. IPPOLITI. Cimetidine, an H_2-antihistamine, stimulates prolactin secretion in man. *J. Clin. Endocrinol. Metab.* 45: 367–370, 1977.
115. CARSWELL, H., P. R. DAUM, AND J. M. YOUNG. Histamine H_1-agonist stimulated breakdown of inositol phospholipids. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 27–38.
116. CARSWELL, H., A. G. GALIONE, AND J. M. YOUNG. Differential effect of temperature on histamine- and carbachol-stimulated inositol phospholipid breakdown in slices of guinea-pig cerebral cortex. *Br. J. Pharmacol.* 90: 175–182, 1987.
117. CARSWELL, H., AND S. R. NAHORSKI. Distribution and characteristics of histamine H_1-receptors in guinea-pig airways [identified by [^{3}H]mepyramine. *Eur. J. Pharmacol.* 81: 301–307, 1982.
118. CHALMERS, J. P., P. R. C. HOWE, J. C. PROVIS, AND M. J. WEST. Cardiac and central histamine in spontaneously hypertensive and stroke-prone rats. In: *Nervous System and Hypertension*, edited by P. Meyer and H. Schmitt. New York: Wiley, 1979, p. 244–251.
119. CHANG, R. S. L., AND S. H. SNYDER. Histamine H_1-receptor binding sites in guinea pig brain membranes: regulation of agonist interactions by guanine nucleotides and cations. *J. Neurochem.* 34: 916–923, 1980.
120. CHANG, R. S. L., V. T. TRAN, AND S. H. SNYDER. Histamine H_1-receptors in brain labeled with [^{3}H]-mepyramine. *Eur. J. Pharmacol.* 48: 463–464, 1978.
121. CHANG, R. S. L., V. T. TRAN, AND S. H. SNYDER. Heterogeneity of histamine H_1-receptors: species variations in [^{3}H]-mepyramine binding of brain membranes. *J. Neurochem.* 32: 1653–1663, 1979.
122. CHANG, R. S. L., V. T. TRAN, AND S. H. SNYDER. Neurotransmitter receptor localizations: brain lesion induced alterations in benzodiazepine, GABA, β-adrenergic and histamine H_1-receptor binding. *Brain Res.* 190: 95–110, 1980.
123. CHARLI, J. L., P. JOSEPH-BRAVO, J. M. PALACIOS, AND C. KORDON. Histamine-induced release of thyrotropin releasing hormone from hypothalamic slices. *Eur. J. Pharmacol.* 52: 401–403, 1978.
124. CHEW, C. S. Parietal cell protein kinases. Selective activation of type I cAMP-dependent protein kinase by histamine. *J. Biol. Chem.* 260: 7540–7550, 1985.
125. CHEW, C. S., AND M. R. BROWN. Histamine increases phosphorylation of 27- and 40-kDa parietal cell proteins. *Am. J. Physiol. 253 (Gastrointest. Liver Physiol. 16)*: G823–G829, 1987.
126. CHRONISTER, R. P., G. C. PALMER, J. P. DE FRANCE, R. W. SIKES, AND J. I. HUBBARD. Histamine: correlative studies in nucleus accumbens. *J. Neurobiol.* 13: 23–38, 1982.
127. CHUDOMELKA, P. J., AND L. C. MURRIN. Transport of histidine into synaptosomes of the rat central nervous system. *J. Neurochem.* 40: 830–835, 1983.
128. CHUNG, Y. H., H. MIYAKE, C. KAMEI, AND K. TASAKA. Analgesic effect of histamine induced by intracerebral injection into mice. *Agents Actions* 15: 137–142, 1984.
129. CLARK, R. B., AND J. P. PERKINS. Regulation of adenosine 3',5'-monophosphate concentration in cultured human astrocytoma cells by catecholamines and histamine. *Proc. Natl. Acad. Sci. USA* 68: 2757–2760, 1971.
130. CLARK, W. G., AND H. R. CUMBY. Biphasic changes in body temperature produced by intracerebroventricular injections of histamine in the cat. *J. Physiol. Lond.* 261: 235–253, 1976.
131. CLARO, E., L. ARBONES, A. GARCIA, AND F. PICATOSTE. Phosphoinositide hydrolysis mediated by histamine H_1-receptors in rat brain cortex. *Eur. J. Pharmacol.* 123: 187–196, 1986.
132. CLARO, E., A. GARCIA, AND F. PICATOSTE. Histamine-stimulated phosphoinositide hydrolysis in developing rat brain. *Mol. Pharmacol.* 32: 384–390, 1987.
133. CLINESCHMIDT, B. V., AND V. J. LOTTI. Histamine: intraventricular injection suppresses ingestive behavior of the cat. *Arch. Int. Pharmacodyn. Ther.* 206: 288–298, 1973.
134. CODOLA, R., AND A. GARCIA. Effect of thyroid state on histamine H_1-receptors in adult and developing rat brain. *Biochem. Pharmacol.* 34: 4131–4136, 1985.

135. COHEN, P., A. BURCHELL, J. G. FOULKES, AND P. T. W. COHEN. Identification of the Ca^{2+}-dependent modulator protein as the fourth subunit of rabbit skeletal muscle phosphorylase kinase. *FEBS Lett.* 92: 287-293, 1978.

136. COHN, C. K., G. G. BALL, AND J. HIRSCH. Histamine: effect of self-stimulation. *Science Wash. DC* 180: 757-758, 1973.

137. COLBOC, O., P. PROTAIS, AND J. COSTENTIN. Histamine-induced rise in core temperature of chloral-anaesthetized rats: mediation by H_2-receptors located in the preoptican area of hypothalamus. *Neuropharmacology* 21: 45-50, 1982.

137a. COOPER, D. G., R. C. YOUNG, G. J. DURANT, AND C. R. GANELLIN. Histamine receptors. In: *Comprehensive Medicinal Chemistry*, edited by P. G. Sammes and J. B. Taylor. Oxford, UK: Pergamon, 1990, p. 323-421.

138. CORREA, F. M. A., AND J. M. SAAVEDRA. Increase in histamine concentrations in discrete hypothalamic nuclei of spontaneously hypertensive rats. *Brain Res.* 205: 445-451, 1981.

139. CORREA, F. M. A., AND J. M. SAAVEDRA. High histamine levels in specific hypothalamic nuclei of Brattleboro rats lacking vasopressin. *Brain Res.* 276: 247-252, 1983.

140. COSTENTIN, J., J. M. ANDRE, J. C. SCHWARTZ, AND R. BOULU. Histamine endogène et thermorégulation. *C. R. Seances Soc. Biol. Paris* 166: 1366-1369, 1972.

141. COSTENTIN, J., R. BOULU, AND J. C. SCHWARTZ. Pharmacological studies on the role of histamine in thermoregulation. *Agents Actions* 3: 177, 1973.

142. COSTENTIN, J., J. C. SCHWARTZ, AND R. BOULU. Behavioural effects of histidine loads. *J. Pharmacol.* 5: 195-208, 1974.

143. COX, B., M. D. GREEN, W. CHESAREK, AND P. LOMAX. The effect of 4-methyl-histamine on temperature regulation in the rat. *J. Therm. Biol.* 1: 205-207, 1976.

144. COX, B., M. D. GREEN, AND P. LOMAX. Thermoregulatory effects of histamine. *Experientia Basel* 32: 498-500, 1976.

145. COX, B., AND P. LOMAX. Pharmacologic control of temperature regulation. *Annu. Rev. Pharmacol. Toxicol.* 17: 341-353, 1977.

146. CRAWFORD, M. L. A., AND M. YOUNG. $GABA_B$ receptor-mediated inhibition of histamine H_1-receptor induced inositol phosphate formation in slices of rat cerebral cortex. *J. Neurochem.* 51: 1441-1447, 1988.

147. CREVELING, C. R., E. T. MCNEAL, D. H. MCCULLOCH, AND J. W. DALY. Membrane potentials in cell-free preparations from guinea pig cerebral cortex: effect of depolarizing agents and cyclic nucleotides. *J. Neurochem.* 35: 922-932, 1980.

148. CROOK, R. B., M. B. FARBER, AND S. B. PRUSINER. H_2 histamine receptors on the epithelial cells of choroid plexus. *J. Neurochem.* 46: 489-493, 1986.

149. CYBULSKY, D. L., S. I. KANDEL, J. W. WELLS, AND A. G. GORNALL. Guanylylimidodiphosphate modulates [^{3}H]histamine binding in a solubilised preparation from rat brain. *Eur. J. Pharmacol.* 72: 407-409, 1981.

150. DACEY, R. G., AND J. E. BASSETT. Histaminergic vasodilatation of intracerebral arterioles in the rat. *J. Cereb. Blood Flow Metab.* 7: 327-331, 1987.

151. DALE, H. H., AND P. P. LAIDLAW. The physiological action of β-iminazolylethylamine. *J. Physiol. Lond.* 41: 318-344, 1910.

152. DALE, H. H., AND P. P. LAIDLAW. Further observations on the action of β-iminazolylethylamine. *J. Physiol. Lond.* 43: 182-195, 1911.

153. DALY, J. W. Accumulation of cyclic nucleotides. In: *Cyclic Nucleotides in the Nervous System*, edited by J. W. Daly. New York: Plenum, 1977, p. 97-209.

154. DALY, J. W., E. MCNEAL, C. PARTINGTON, M. NEUWIRTH, AND C. R. CREVELING. Accumulations of cyclic AMP in adenine-labeled cell-free preparations from guinea pig cerebral cortex: role of α-adrenergic and H_1-histaminergic receptors. *J. Neurochem.* 35: 326-337, 1980.

155. DALY, J. W., W. PADGETT, AND K. B. SEAMON. Activation of cyclic AMP-generating systems in brain membranes and slices by the diterpene forskolin: augmentation of receptor-mediated responses. *J. Neurochem.* 38: 532-544, 1982.

156. DAM TRUNG TUONG, M., M. GARBARG, AND J. C. SCHWARTZ. Pharmacological specificity of brain histamine H_2-receptors differs in intact cells and cell-free preparations. *Nature Lond.* 287: 548-551, 1980.

157. DANOFF, S., AND J. M. YOUNG. Is histamine potentiation of adenosine-stimulated cyclic AMP accumulation in guinea-pig cerebral cortical slices mediated by products of inositol phospholipid breakdown? *Biochem. Pharmacol.* 36: 1177-1179, 1987.

158. DAUM, P. R., C. P. DOWNES, AND J. M. YOUNG. Histamine-induced inositol phospholipid breakdown mirrors H_1-receptor density in brain. *Eur. J. Pharmacol.* 87: 497-498, 1983.

159. DAUM, P. R., C. P. DOWNES, AND J. M. YOUNG. Histamine stimulation of inositol 1-phosphate accumulation in lithium-treated slices from regions of guinea pig brain. *J. Neurochem.* 43: 25-32, 1984.

160. DAUM, P. R., S. J. HILL, AND J. M. YOUNG. Histamine H_1-agonist potentiation of adenosine-stimulated cyclic AMP accumulation in slices of guinea-pig cerebral cortex: comparison of response and binding parameters. *Br. J. Pharmacol.* 77: 347-357, 1982.

161. DE ALMEIDA, M., AND I. IZQUIERDO. Memory facilitation by histamine. *Arch. Int. Pharmacodyn. Ther.* 238: 193-198, 1986.

162. DELARBRE, B., H. SCHMITT, AND D. SENON. Effects of activation of H_1- and H_2-receptors on central cardiovascular structures in cats and on behaviour in chickens (Abstract). *Br. J. Pharmacol.* 52: 443P, 1976.

163. DELLE FAVE, G. F., R. CARRATU, L. DE MAGISTRIS, C. NATOLI, M. L. SANTORO, G. TAMBURANO, AND A. TORSOLI. Variations in serum prolactin following cimetidine treatment for peptic ulcer disease. *Gastroenterology* 9: 142-148, 1977.

164. DEVOTO, P., A. M. MARCHISIO, E. CARBONI, AND P. F. SPANO. Detection of [^{3}H]-cimetidine specific binding in rat anterior pituitary. *Eur. J. Pharmacol.* 68: 91-93, 1980.

165. DIEPEN, R. Der hypothalamus. In: *Handbuch der Mikroscopischen Anatomie des Menschen*, edited by W. V. Mollendorf. Berlin: Springer-Verlag, 1962.

166. DIMITRIADOU, V., P. AUBINEAU, J. TAXI, AND J. SEYLAZ. Ultrastructural evidence for a functional unit between nerve fibers and type II cerebral mast cells in the cerebral vascular wall. *Neuroscience* 22: 621-630, 1987.

167. DI RENZO, G. F., V. BASILE, S. AMOROSO, M. TAGLIALATELA, F. MAURANO, AND L. ANNUNZIATO. Possible inhibitory role of histaine H_2 receptors in the control of basal TSH secretion in male rats: studies with dimaprit, a selective H_2 receptor agonist. *J. Neural Transm.* 69: 313-318, 1987.

168. DISMUKES, K., M. J. KUHAR, AND S. H. SNYDER. Brain histamine alterations after hypothalamic isolations. *Brain Res.* 78: 144-151, 1974.

169. DISMUKES, K., M. ROGERS, AND J. W. DALY. Cyclic adenosine 3',5'-monophosphate formation in guinea-pig brain slices: effect of H_1- and H_2-histaminergic agonists. *J. Neurochem.* 26: 785-790, 1976.

170. DISMUKES, K. R., AND S. H. SNYDER. Histamine turnover in rat brain. *Brain Res.* 73: 467-481, 1974.

171. DOGTEROM, J., T. B. VAN WIMERSMA GREIDANUS, AND D. DE WIED. Histamine as an extremely potent releaser of vasopressin in the rat. *Experientia Basel* 32: 659-660, 1976.

172. DONALDSON, J., A. M. BROWN, AND S. HILL. Influence of rolipram on the cyclic 3',5'-adenosine monophosphate response to histamine and adenosine in slices of guinea-pig cerebral cortex. *Biochem. Pharmacol.* 37: 715-723, 1988.

173. DONALDSON, J., AND S. J. HILL. Histamine-induced hydrolysis of polyphosphoinositides in guinea-pig ileum and brain. *Eur. J. Pharmacol.* 124: 255-265, 1986.

174. DONALDSON, J., AND S. J. HILL. Enhancement of histamine H_1-receptor agonist activity by 1,4-dithiothreitol in guinea-pig cerebellum and cerebral cortex. *J. Neurochem.* 47: 1476-1482, 1986.

175. DONALDSON, J., AND S. J. HILL. 1,4-Dithiothreitol-induced changes in histamine H_1-agonist efficacy and affinity in the longitudinal smooth muscle of guinea-pig ileum. *Br. J. Pharmacol.* 90: 263-271, 1987.

176. DONOSO, A. O. Induction of prolactin and luteinising hormone release by histamine in male and female rats and the influence of brain transmitter antagonists. *J. Endocrinol.* 76: 193-202, 1978.

177. DONOSO, A. O. Receptors mediating the facilitatory actions of histamine on prolactin and luteinising hormone release in rats. *Adv. Physiol. Sci.* 14: 179-183, 1980.

178. DONOSO, A. O. The possible role of brain histamine in neuroendocrine and cardiovascular regulation. *Med. Res. Rev.* 6: 365–386, 1986.
179. DONOSO, A. O., AND R. O. ALVAREZ. Brain histamine as neuroendocrine transmitter. *Trends Pharmacol. Sci.* 6: 98–100, 1984.
180. DONOSO, A. O., AND A. M. BANZAN. Acute effects of histamine on plasma prolactin and luteinizing hormone levels in male rats. *J. Neural Transm.* 39: 95–101, 1976.
181. DONOSO, A. O., AND A. M. BANZAN. Failure of histamine to induce the release of luteinizing hormone in castrated rats primed with sex steroids. *J. Endocrinol.* 78: 447–448, 1978.
182. DONOSO, A. O., AND A. M. BANZAN. Release of prolactin and LH and histamine-containing cells in brain. *J. Neural Transm.* 44: 327–332, 1979.
183. DONOSO, A. O., AND A. M. BANZAN. H_1- and H_2-histamine receptor antagonists and induced release of prolactin in male rats. *Neuroendocrinology* 30: 11–14, 1980.
184. DONOSO, A. O., A. M. BANZAN, AND M. I. BORZINO. Prolactin and luteinizing hormone release after intraventricular injection of histamine in rats. *J. Endocrinol.* 68: 171–172, 1976.
185. DONOSO, A. O., AND M. B. ZARATE. Release of prolactin and luteinizing hormone by histamine agonists in ovariectomized, steroid-treated rats under ether anesthesia. *Exp. Brain Res.* 52: 277–280, 1983.
186. DONOSO, A. O., M. B ZARATE, AND A. SELTZER. Histamine-induced prolactin release: pharmacological characterization of receptors in male rats. *Neuroendocrinology* 36: 436–442, 1983.
187. DOUGLAS, W. W. Involvement of calcium in exocytosis and the exocytosis-vesiculation sequence. *Biochem. Soc. Symp.* 39: 1–38, 1974.
188. DOUGLAS, W. W. Histamine and 5-hydroxytryptamine (serotonin) and their antagonists. In: *The Pharmacological Basis of Therapeutics*, edited by A. F. Gilman, L. S. Goodman, and A. Gilman. New York: Macmillan, 1985, p. 604–673.
189. DROPP, J. J. Mast cells in the central nervous system of several rodents. *Anat. Rec.* 174: 227–238, 1972.
190. DROPP, J. J. Mast cells in mammalian brain. *Acta Anat.* 94: 1–21, 1976.
191. DRUMMOND, G. S., S. B. GERTNER, AND M. GOLDSTEIN. Stimulation of brain histidine decarboxylase activity by c-AMP (Abstract). *Federation Proc.* 37: 1630, 1978.
192. DUCH, D. S., S. W. BOWERS, AND C. A. NICHOL. Elevation of brain histamine levels by diamino pyrimidine inhibitors of histamine-*N*-methyl transferase. *Biochem. Pharmacol.* 27: 1507–1509, 1978.
193. DUFY-BARBE, L., D. VERRIER, J. ARSAUT, D. BIOKA, AND B. DUFY. Histamine et libération de prolactine chez le singe rhésus. *C. R. Seances Soc. Biol. Paris* 177: 158–165, 1983.
194. DUGGAN, D. E., D. F. HOOKE, AND A. L. MAYCOCK. Inhibition of histamine synthesis in vitro and in vivo by *S*-α-fluoromethylhistidine. *Biochem. Pharmacol.* 32: 4003–4009, 1984.
195. DURANT, G. J., C. R. GANELLIN, R. GRIFFITHS, C. A. HARVEY, D. A. A. OWEN, AND G. S. SACH. Some newer H_1-receptor histamine antagonists In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 3–11.
196. DUX, E., AND F. JOO. Effects of histamine on brain capillaries. Fine structural and immunohistochemical studies after intracarotid infusion. *Exp. Brain Res.* 47: 252–258, 1982.
197. EA-KIM, L., AND N. OUDART. A highly potent and selective H_2 agonist relaxes rabbit middle cerebral artery, in vitro. *Eur. J. Pharmacol.* 150: 393–396, 1988.
198. EDVINSSON, L., J. CERVOS-NAVARRO, L. J. LARSSON, C. OWMAN, AND A. L. RONNBERG. Regional distribution of mast cells containing histamine, dopamine, or 5-hydroxytryptamine in the mammalian brain. *Neurology* 27: 873–883, 1977.
200. EDVINSSON, L., P. M. GROSS, AND A. MOHAMED. Characterization of histamine receptors in rat cerebral arteries in vitro and in situ. *J. Pharmacol. Exp. Ther.* 225: 168–175, 1983.
201. EDVINSSON, L., AND C. OWMAN. A pharmacological comparison of histamine receptors in isolated extracranial and intracranial arteries in vitro. *Neurology* 25: 271–276, 1975.
202. EDVINSSON, L., C. H. OWMAN, AND N. O. SJOBERG. Autonomic nerves, mast cells, and amine receptors in human brain vessels. A histochemical and pharmacological study. *Brain Res.* 115: 377–393, 1976.
203. EDWARDS, C., S. R. NAHORSKI, AND K. J. ROGERS. In vivo changes of cerebral cyclic adenosine 3′,5′ monophosphate induced by biogenic amines: association with phosphorylase activation. *J. Neurochem.* 22: 565–572, 1974.
204. EL-ACKAD, T. M., AND M. J. BRODY. Fluorescence histochemical localization of non mast-cell histamine. In: *Neuropsychopharmacology*, edited by J. R. Boissier, H. Hippius, and P. Pichot. New York: Elsevier, 1975, p. 551–559.
205. ENDO, Y. Elevation of histamine levels in rat and mouse tissues by the deacetylation of administered *N*-acetylhistamine. *Eur. J. Pharmacol.* 60: 299–306, 1979.
206. ENERBACK, L. Mast cell heterogeneity: the evolution of the concept of a specific mucosal mast cell. In: *Mast Cell Differentiation and Heterogeneity*, edited by A. D. Befus, J. Bienenstock, and J. A. Denburg. New York: Raven, 1986, p. 1–26.
207. ERICSON, H., T. WATANABE, AND C. KOHLER. Morphological analysis of the tuberomammillary nucleus in the rat brain: delineation of subgroups with antibody against L-histidine decarboxylase as a marker. *J. Comp. Neurol.* 263: 1–24, 1987.
208. FAINGOLD, C. L. Antihistaminics as central nervous system depressants. In: *Handbook of Experimental Pharmacology, Histamine and Anti-Histaminics*, edited by M. Rocha e Silva. Berlin: Springer-Verlag, 1978, vol. 18, pt. 2, p. 561–573.
209. FALASCHI, P., S. RUGGIERI, R. D'URSO, A. ROCCO, E. SCARNATI, C. FORCHETTI, M. BOGHEN, G. FRAJESE, AND A. AGNOLI. Further evidence for a role of histamine H_2 receptor in controlling prolactin secretion. In: *Central and Peripheral Regulation of Prolactin Function*, edited by R. M. MacLeod and U. Scapagnini. New York: Raven, 1980, p. 261–264.
210. FEHM, H. L., K. H. VOIGT, R. E. LANG, AND E. F. PFEIFFER. Effects of neurotransmitters on the release of corticotropin releasing hormone (CRH) by rat hypothalamic tissue in vitro. *Exp. Brain Res.* 39: 229–234, 1980.
211. FELDBERG, W. The action of histamine on the blood vessels of the rabbit. *J. Physiol. Lond.* 63: 211–221, 1927.
212. FELDBERG, W. Histamine and anaphylaxis. *Annu. Rev. Physiol.* 8: 671–694, 1941.
213. FERRER, I., F. PICATOSTE, E. RODERGAS, A. GARCIA, J. SABRIA, AND I. BLANCO. Histamine and mast cells in developing rat brain. *J. Neurochem.* 32: 587–592, 1979.
214. FINCH, L., AND P. E. HICKS. The cardiovascular effects of intraventricularly administered histamine in the anesthetised rat. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 293: 151–157, 1976.
215. FINCH, L., AND P. E. HICKS. Central hypertensive action of histamine in conscious normotensive cats. *Eur. J. Pharmacol.* 36: 263–266, 1976.
216. FINCH, L., AND P. E. HICKS. Involvement of hypothalamic histamine receptors in the central cardiovascular actions of histamine. *Neuropharmacology* 16: 211–218, 1977.
217. FOREMAN, J. C., D. R. NORRIS, T. J. RISING, AND S. E. WEBER. The binding of [^{3}H] tiotidine to homogenates of guinea pig lung parenchyma. *Br. J. Pharmacol.* 86: 475–482, 1985.
218. FORN, J., AND G. KRISHNA. Effect of norepinephrine, histamine and other drugs on cyclic 3′:5′-AMP formation in brain slices of various animals species. *Pharmacology* 8: 193–204, 1971.
219. FRANCIS, D. M., M. F. THOMPSON, AND M. W. GREAVES. The kinetic properties and reaction mechanism of histamine methyltransferase from human skin. *Biochem. J.* 137: 819–828, 1980.
220. FRIEDEL, R. O., AND S. M. SCHANBERG. Effect of histamine on phospholipid metabolism of rat brain in vivo. *J. Neurochem.* 24: 819–820, 1975.
221. FROSTHOLM, A., AND A. ROTTER. Autoradiographic localization of receptors in the cochlear nucleus of the mouse. *Brain Res. Bull.* 16: 189–293, 1986.
222. FUCHS, V., AND H. COPER. The influence of antihistamine compounds on the oral intake of different addictive drugs. *Drug Alcohol Depend.* 17: 359–364, 1986.
223. FUKUI, H., N. P. WANG, T. WATANABE, AND H. WADA. Solubilization, characterization and partial purification of [^{3}H] mepyramine-binding protein, a possible histamine H_1 receptor, from rat liver membrane. *Jpn. J. Pharmacol.* 46: 127–139, 1988.
224. FUKUI, H., T. WATANABE, AND H. WADA. Immunochemical

cross reactivity of the antibody elicited against L-histidine decarboxylase purified from the whole bodies of fetal rat with the enzyme from rat brain. *Biochem. Biophys. Res. Commun.* 93: 333–339, 1980.

225. GAJTKOWSKI, G. A., D. B. NORRIS, T. J. RISING, AND T. P. WOOD. Specific binding of [^{3}H]-tiotidine to histamine H_2 receptors in guinea pig cerebral cortex. *Nature Lond.* 304: 65–67, 1983.
226. GANELLIN, C. R. Chemistry and structure activity relationship of drugs acting at histamine receptors. In: *Pharmacology of Histamine Receptors*, edited by C. R. Ganellin and M. E. Parsons. Bristol, UK: Wright, 1982, p. 10–102.
227. GANELLIN, C. R., AND M. E. PARSONS (Editors). *Pharmacology of Histamine Receptors.* Bristol, UK: Wright, 1982.
228. GANELLIN, C. R., AND J. C. SCHWARTZ (Editors). *Frontiers in Histamine Research. Advances in the Biosciences*, Oxford, UK: Pergamon, 1985, vol. 51.
229. GANNON, M. N., AND L. B. HOUGH. Properties of a [^{3}H]-adenine-prelabeled vesicular preparation from guinea pig cerebral cortex: optimization of incubation conditions for basal and histamine-stimulated [^{3}H]-cAMP levels. *J. Pharmacol. Methods* 16: 315–328, 1986.
230. GANNON, M. N., AND L. B. HOUGH. Histamine receptors coupled to [^{3}H]cAMP accumulation in brain: pharmacological characterization in a vesicular preparation of guinea pig cortex. *Mol Pharmacol.* 33: 44–50, 1988.
231. GARBARG, M., G. BARBIN, S. BISCHOFF, H. POLLARD, AND J. C. SCHWARTZ. Dual localization of histamine in an ascending neuronal pathway and in non-neuronal cells evidenced by lesions in the lateral hypothalamic area. *Brain Res.* 106: 333–348, 1976.
232. GARBARG, M., G. BARBIN, J. FEGER, AND J. C. SCHWARTZ. Histaminergic pathway in rat brain evidenced by lesions of the MFB. *Science Wash. DC* 186: 833–835, 1974.
233. GARBARG, M., G. BARBIN, C. LLORENS, J. M. PALACIOS, H. POLLARD, AND J. C. SCHWARTZ. Recent development in brain histamine research: pathways and receptors. In: *Neurotransmitters, Receptors, and Drug Action*, edited by W. B. Essman. New York: Spectrum, 1980, p. 179–202.
234. GARBARG, M., G. BARBIN, J. M. PALACIOS, AND J. C. SCHWARTZ. Effects of kainic acid on histaminergic systems in guinea pig hippocampus. *Brain Res.* 150: 638–641, 1978.
235. GARBARG, M., G. BARBIN, E. RODERGAS, AND J. C. SCHWARTZ. Inhibition of histamine synthesis in brain by α-fluoromethylhistidine, a new irreversible inhibitor: in vitro and in vivo studies. *J. Neurochem.* 35: 1045–1052, 1980.
236. GARBARG, M., M. BAUDRY, P. BENDA, AND J. C. SCHWARTZ. Simultaneous presence of histamine-*N*-methyltransferase and catechol-O-methyltransferase in neuronal and glial cells in culture. *Brain Res.* 81: 61–64, 1974.
237. GARBARG, M., K. M. KRISHNAMOORTHY, J. FEGER, AND J. C. SCHWARTZ. Effects of mesencephalic and hypothalamic lesions on histamine levels in rat brain. *Brain Res.* 50: 361–367, 1973.
238. GARBARG, M., H. POLLARD, T. T. QUACH, AND J. C. SCHWARTZ. Methods in brain histamine research. In: *Methods in Biogenic Amine Research*, edited by S. Parvez, T. Nagatsu, I. Nagatsu, and H. Parvez. Amsterdam: Elsevier, 1983, p. 623–662.
238a. GARBARG, M., H. POLLARD, M. D. TRUNG TUONG, J. C. SCHWARTZ, AND C. GROS. Sensitive radioimmunoassays for histamine and *tele*-methylhistamine in the brain. *J. Neurochem.* 53: 1724–1730, 1989.
238b. GARBARG, M., AND J. C. SCHWARTZ. Synergism between histamine H_1- and H_2-receptors in the cAMP response in guinea pig brain slices: effects of phorbol esters and calcium. *Mol. Pharmacol.* 33: 38–43, 1988.
239. GARBARG, M., M. D. TRUNG TUONG, C. GROS, AND J. C. SCHWARTZ. Effects of histamine H_2-receptor ligands on various biochemical indices of histaminergic neuron activity in rat brain. *Ann. J. Pharmacol.* 164: 1–11, 1989.
240. GARBARG, M., E. YERAMIAN, M. KÖRNER, AND J. C. SCHWARTZ. Biochemical studies of cerebral H_1-receptors. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 19–25.
241. GATTI, P. J., AND S. B. GERTNER. The effect of a vasopressin antagonist on the pressin response to histamine administered centrally. *Neuropharmacology* 22: 895–902, 1983.
242. GATTI, P. J., AND S. B. GERTNER. Cardiovascular and behavioral actions of centrally administered cimetidine. *J. Cardiovasc. Pharmacol.* 6: 575–581, 1984.
243. GAVISH, M., R. S. L. CHANG, AND S. H. SNYDER. Solubilization of histamine H_1, GABA and benzodiazepine receptors. *Life Sci.* 2: 793–799, 1979.
244. GELLER, H. M. Effects of some putative neurotransmitters on unit activity of tuberal hypothalamic neurons in vitro. *Brain Res.* 108: 423–430, 1976.
245. GELLER, H. M. Are histamine H_2-receptor depressions of neuronal activity in tissue cultures from rat hypothalamus mediated through cyclic adenosine monophosphate? *Neurosci. Lett.* 14: 49–53, 1979.
246. GELLER, H. M. Histamine actions on activity of cultured hypothalamic neurons: evidence for mediation by H_1-and H_2-histamine receptors. *Dev. Brain Res.* 1: 89–101, 1981.
247. GERALD, M. C., AND R. P. MAICKEL. Studies on the possible role of brain histamine in behaviour. *Br. J. Pharmacol.* 44: 462–471, 1972.
248. GIBBS, D. M., P. M. PLOTSKY, W. J. DE GREEF, AND J. D. NEILL. Effect of histamine and acetylcholine on hypophyseal stalk plasma dopamine and peripheral plasma prolactin levels. *Life Sci.* 24: 2063–2070, 1979.
249. GLICK, S. D., AND L. A. CRANE. Opiate-like and abstinence-like effects of intracerebral histamine administration in rats. *Nature Lond.* 273: 547–549, 1978.
250. GOGAS, K. R., AND L. B. HOUGH. Effects of solantidine, a brain-penetrating H_2-receptor antagonist, on naloxone-sensitive and naloxone-resistant analgesia. *Neuropharmacology* 27: 357–362, 1988.
251. GOLDSCHMIDT, R. C., L. B. HOUGH, S. O. GLICK, AND J. PADAWER. Mast cells in rat thalamus: nuclear localization, sex difference and left-right asymmetry. *Brain Res.* 323: 209–217, 1984.
252. GOLDSTEIN, M., AND L. A. GREENE. Activation of tyrosine hydroxylase by phosphorylation. In: *Psychopharmacology: The Third Generation of Progress*, edited by H. Y. Meltzer. New York: Raven, 1987, p. 75–80.
253. GRANATA, A. R., AND D. J. REIS. Hypotension and bradycardia elicited by histamine into the C_1 area of the rostral ventrolateral medulla. *Eur. J. Pharmacol.* 136: 167–182, 1987.
254. GREEN, J. P. Histamine. In: *Handbook of Neurochemistry, Control Mechanisms in the Nervous System*, edited by A. Lajtha. New York: Plenum, 1970, vol. 4, p. 221–250.
255. GREEN, J. P. Histamine receptors in brain. In: *Handbook of Psychopharmacology*, edited by L. Iversen, S. D. Iversen, and S. H. Snyder. New York: Plenum, 1983, vol. 17, p. 395–420.
256. GREEN, J. P. Histamine receptors. In: *Psychopharmacology: The Third Generation of Progress*, edited by H. Y. Meltzer. New York: Raven, 1987, p. 273–279.
257. GREEN, J. P., C. L. JOHNSON, H. WEINSTEIN, AND S. MAAYANI. Antagonism of histamine activated adenylate cyclase in brain by D-lysergic acid diethylamide. *Proc Natl. Acad. Sci. USA* 74: 5697–5701, 1977.
258. GREEN, J. P., AND J. K. KHANDELWAL. Histamine turnover in regions of rat brain. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 185–195.
259. GREEN, J. P., AND S. MAAYANI. Tricyclic antidepressant drugs block histamine H_2-receptor in brain. *Nature Lond.* 269: 163–165, 1977.
260. GREEN, M. D., B. COX, AND P. LOMAX. Sites and mechanisms of action of histamine in the central thermoregulatory pathways on the rat. *Neuropharmacology* 15: 321–324, 1976.
261. GROSS, P. M. Hypothesis: histamine H_1- and H_2-receptors are differentially and spatially distributed in cerebral vessels. *J. Cereb. Blood Flow Metab.* 1: 441–446, 1981.
262. GROSS, P. M. Cerebral histamine: indications for neuronal and vascular regulation. *J. Cereb. Blood Flow Metab* 2: 3–23, 1982.
263. GROSS, P. M. Multiple actions of histamine on cerebral blood

vessels. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 341–349.
264. GROSS, P. M., A. M. HARPER, AND C. M. TEASDALE. Cerebral circulation and histamine. 2. Responses of pial veins and arterioles to receptor agonists. *J. Cereb. Blood Flow Metab.* 1: 219–225, 1981.
265. GROSS, P. M., A. M. HARPER, AND C. M. TEASDALE. Cerebral circulation and histamine. 1. Participation of vascular H_1- and H_2-receptors in vasodilatory responses to carotid arterial infusion. *J. Cereb. Blood Flow Metab.* 1: 97–108, 1981.
266. GROSS, P. M., A. M. HARPER, AND G. M. TEASDALE. Impromidine, a potent dilator of cat pial arterioles. *Eur. J. Pharmacol.* 73: 225–227, 1981.
267. GROSS, P. M., G. M. TEASDALE, D. I. GRAHAM, W. J. ANGERSON, AND A. M. HARPER. Intra-arterial histamine increases blood-brain transport in rats. *Am. J. Physiol.* 243 (*Heart Circ. Physiol.* 12): H307–H317, 1982.
268. GRZANNA, R. Histidine decarboxylase: isolation and molecular characteristics. *Neurochem. Res.* 90: 993–1009, 1984.
269. GRZANNA, R., AND L. D. SHULTZ. The contribution of mast cells to the histamine content of the central nervous system: a regional analysis. *Life Sci.* 30: 1959–1964, 1982.
270. GULAT-MARNAY, C., A. LAFITTE, J. M. ARRANG, AND J. C. SCHWARTZ. Regulation of histamine release and synthesis in the brain by muscarinic receptors. *J. Neurochem.* 52: 248–254, 1989.
271. GULAT-MARNAY, C., A. LAFITTE, J. M. ARRANG, AND J. C. SCHWARTZ. Modulation of histamine release and synthesis in the brain mediated by alpha-2 adrenoceptors. *J. Neurochem.* 53: 519–524, 1989.
271a. GULAT-MARNAY, C., A. LAFITTE, J. M. ARRANG, AND J. C. SCHWARTZ. Modulation of histamine release in the rat brain by kappa-opioid receptors. *J. Neurochem.* 55: 47–53, 1990.
272. HAAS, H. L. Histamine action on single hypothalamic neurons. *Brain Res.* 76: 363–366, 1974.
273. HAAS, H. L. Histamine hyperpolarizes hippocampal neurones in vitro. *Neurosci. Lett.* 22: 75–78, 1981.
274. HAAS, H. L. Histamine in the central nervous system. Histamine potentiates neuronal excitation by blocking a calcium-dependent potassium conductance. *Agents Actions* 14: 534–537, 1984.
275. HAAS, H. L. Histamine may act through cyclic AMP on hippocampal neurones. *Agents Actions* 16: 234–235, 1985.
276. HAAS, H. L. Histamine actions in the mammalian central nervous system. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 215–224.
277. HAAS, H. L. Histamine. In: *Neurotransmitter Actions in the Vertebrate Nervous System*, edited by M. A. Rogawski and J. L. Barker. New York: Plenum, 1985, p. 321–337.
278. HAAS, H. L., E. G. ANDERSON, AND L. HÖSLI. Histamine and metabolites: their effects and interactions with convulsants on brain stem neurons. *Brain Res.* 51: 269–278, 1973.
279. HAAS, H. L., AND U. M. BUCHER. Histamine H_1-receptors on single central neurones. *Nature Lond.* 255: 634–635, 1975.
280. HAAS, H. L., AND R. W. GREENE. Effects of histamine on hippocampal pyramidal cells of the rat in vitro. *Exp. Brain Res.* 62: 123–130, 1986.
281. HAAS, H. L., L. HÖSLI, E. G. ANDERSON, AND P. WOLF. Action of histamine and metabolites on single neurones of the mammalian central nervous system. In: *Neuropsychopharmacology*, edited by J. R. Boissier, H. Hippius, and P. Pichot. Amsterdam: Elsevier/North-Holland, 1975, p. 589–596.
282. HAAS, H. L., J. G. R. JEFFERYS, N. T. SLATER, AND D. O. CARPENTER. Modulation of low calcium induced field bursts in the hippocampus by monoamines and cholinomimetics. *Pfluegers Arch.* 400: 28–33, 1984.
283. HAAS, H. L., AND A. KONNERTH. Histamine and noradrenaline decrease calcium-activated potassium conductance in hippocampal pyramidal cells. *Nature Lond.* 302: 432–433, 1983.
284. HAAS, H. L., AND P. WOLF. Possible histaminergic pathways in the cat and rat brain. *Pfluegers Arch.* 362: 38, 1976.
285. HAAS, H. L., AND P. WOLF. Central actions of histamine: microelectrophoretic studies. *Brain Res.* 122: 269–279, 1977.
286. HAAS, H. L., P. WOLF, J. M. PALACIOS, M. GARBARG, G. BARBIN, AND J. C. SCHWARTZ. Hypersensitivity to histamine in the guinea-pig brain: microiontophoretic and biochemical studies. *Brain Res.* 156: 275–291, 1978.
287. HALL, H., AND S. O. ÖGREN. Effects of antidepressant drugs on different receptors in the brain. *Eur. J. Pharmacol.* 70: 393–407, 1981.
288. HALL, H., AND S. O. ÖGREN. Effect of antidepressant drugs on histamine H_1-receptors in the brain. *Life Sci.* 34: 597–605, 1984.
289. HALL, I. P., AND S. J. HILL. β-Adrenoceptor stimulation inhibits histamine-stimulated inositol phospholipid hydrolysis in bovine tracheal smooth muscle. *Br. J. Pharmacol.* 95: 1204–1212, 1988.
290. HAMMAR, L. Mammalian histidine decarboxylase, stability studies with special reference to the effect of salts. *Arch. Dermatol. Res.* 266: 285–294, 1979.
291. HAMMAR, L. Mammalian histidine decarboxylase: effect by protein kinase on mouse mastocytoma histidine decarboxylase. *Agents Actions* 13: 246–249, 1983.
292. HAMMAR, L., S. PAHLMAN, AND S. HJERTEN. Chromatographic purification of a mammalian histidine decarboxylase on charged and non-charged alkyl derivatives of agarose. *Biochim. Biophys. Acta* 403: 554–562, 1975.
293. HARVIMA, R. J., E. O. KAJANDER, I. T. HARVIMA, AND J. E. FRAKI. Purification and partial characterization of rat kidney histamine-*N*-methyltransferase. *Biochim. Biophys. Acta* 841: 42–49, 1985.
294. HAYASHI, H., H. TAKAGI, N. TAKEDA, Y. KUBOTA, M. TOHYAMA, T. WATANABE, AND H. WADA. Fine structure of histaminergic neurons in the caudal magnocellular nucleus of the rat as demonstrated by immunocytochemistry using histidine decarboxylase as a marker. *J. Comp. Neurol.* 229: 233–241, 1984.
295. HAYASHI, H., S. TANASE, AND E. E. SNELL. Pyridoxal 5-phosphate-dependent histidine-decarboxylase. Inactivation by α-fluoromethylhistidine and comparative sequences at the inhibitor and coenzyme-binding sites. *J. Biol. Chem.* 261: 11003–11009, 1986.
296. HEGSTRAND, L. R. Partial characterization of histidine decarboxylase in hamster and rat brain employing a new method. *Neurochem. Res.* 10: 1247–1260, 1985.
297. HEGSTRAND, L. R., AND T. H. KALINKE. Properties of *N*-acetyl-histamine deacetylase in mammalian brain. *J. Neurochem.* 45: 300–307, 1985.
298. HEGSTRAND, L. R., P. D. KANOF, AND P. GREENGARD. Histamine sensitive adenylate cyclase in mammalian brain. *Nature Lond.* 260: 163–165, 1976.
299. HEGSTRAND, L. R., AND J. R. SIMON. Histidine transport into rat brain synaptosomes. *J. Neurochem.* 45: 407–414, 1985.
300. HERKENHAM, M. Mismatches between neurotransmitter and receptor localizations in brain: observations and implications. *Neuroscience* 23: 1–38, 1987.
301. HERVATIN, F., J. M. ARRANG, A. BADO, M. DUBRASQUET, AND M. J. M. LEWIN. Involvement of histamine H_2 receptors in pentagastrin stimulation of gastric acid secretion in the cat (Abstract). *Proc. Chin. Acad. Med. Sci. Peking Union Med. Coll.* 3: A25, 1988.
302. HERVATIN, F., M. DUBRASQUET, A. BADO, AND M. J. M. LEWIN. Histamine H_2 receptors in the regulation of gastric acid secretion (Abstract). *Biomed. Res.* 9: P216, 1988.
303. HICKS, P. E. Central cardiovascular actions of histamine in rats: involvement of histamine H_2 receptors. *Clin. Exp. Hypertens.* 1: 251–265, 1978.
304. HILL, S. J. Histamine receptors in the mammalian central nervous system: biochemical studies. In: *Progress in Medicinal Chemistry*, edited by G. P. Ellis and G. B. West. Amsterdam: Elsevier, 1987, vol. 24, p. 29–84.
305. HILL, S. J. Histamine receptors branch out. *Nature Lond.* 327: 104–105, 1987.
306. HILL, S. J., P. DAUM, AND J. M. YOUNG. Affinities of histamine H_1-antagonists in guinea pig brain: similarity of values determined from [^{3}H] mepyramine binding and from inhibition of a functional response. *J. Neurochem.* 37: 1357–1360, 1981.

307. HILL, S. J., P. C. EMSON, AND J. M. YOUNG. The binding of [^{3}H] mepyramine to histamine H_1 receptors in guinea-pig brain. *J. Neurochem.* 31: 997–1004, 1978.
308. HILL, S. J., AND D. A. KENDALL. Adenosine augments histamine induced inositol phospholipid in guinea-pig cerebral cortical slices. *Br. J. Pharmacol.* 89: 771–775, 1987.
309. HILL, S. J., AND D. A. KENDALL. Studies on the adenosine-receptor mediating the augmentation of histamine-induced inositol phospholipid hydrolysis in guinea-pig cerebral cortex. *Br. J. Pharmacol.* 91: 661–669, 1987.
310. HILL, S. J., AND R. M. STRAW. α_2-Adrenoceptor-mediated inhibition of histamine release from rat cerebral cortical slices. *Br. J. Pharmacol.* 95: 1213–1219, 1988.
311. HILL, S. J., AND J. M. YOUNG. Histamine H_1-receptors in the brain of the guinea-pig and the rat: differences in ligand binding properties and regional distribution. *Br. J. Pharmacol.* 68: 687–696, 1980.
312. HILL, S. J., AND J. M. YOUNG. Noradrenaline and (*R*)*e*-methylhistamine inhibit the release of [^{3}H]histamine from rat cerebral cortical slices (Abstract). *Br. J. Pharmacol.* 93: 90P, 1988.
313. HILL, S. J., J. M. YOUNG, AND D. H. MARRIAN. Specific binding of ^{3}H-mepyramine to histamine H_1 receptors in intestinal smooth muscle. *Nature Lond.* 270: 361–363, 1977.
314. HILLHOUSE, E. W., J. BURDEN, AND M. T. JONES. The effect of various putative neurotransmitters on the release of corticotrophin releasing hormone from the hypothalamus of the rat in vitro. Effect of acetylcholine and noradrenaline. *Neuroendocrinology* 17: 1–11, 1975.
315. HINE, R. J., M. W. ORSINI, AND L. R. HEGSTRAND. Brain histamine levels in the hamster during the estrous cycle and on selected days of pregnancy. *Neuroendocrinology* 43: 273–276, 1986.
316. HIRATA, F., AND J. AXELROD. Phospholipid methylation and biological signal transmission. *Science Wash. DC* 209: 1082–1090, 1980.
317. HOFFMAN, W. E., AND P. G. SCHMID. Cardiovascular and antidiuretic effects of central histamine. *Life Sci.* 22: 1709–1714, 1978.
318. HOKIN, L. E. Receptors and phosphoinositide generated second messengers. *Annu. Rev. Biochem.* 54: 205–235, 1985.
319. HOLAK, H. A., BALDYS, B. JARZAB, A. WYSTRYCHOWSKI, AND J. SKRZYPEK. Changes in serum TSH level after intraventricular injection of various neuromediators in rats. *Acta Endocrinol.* 87: 279–282, 1978.
320. HOLLINGSWORTH, E. B., AND J. W. DALY. Accumulation of inositol phosphates and cyclic AMP in guinea-pig cerebral cortical preparations. Effects of norepinephrine, histamine carbamylcholine and 2-chloroadenosine. *Biochim. Biophys. Acta* 847: 207–216, 1985.
321. HOLLINGSWORTH, E. B., R. A. DE LA CRUZ, AND J. W. DALY. Accumulations of inositol phosphates and cyclic AMP in brain slices: synergistic interactions of histamine and 2-chloroadenosine. *Eur. J. Pharmacol.* 122: 45–50, 1986.
322. HOLLINGSWORTH, E. B., E. T. MCNEAL, J. L. BURTON, R. J. WILLIAMS, J. W. DALY, AND C. R. CREVELING. Biochemical characterization of a filtered synaptoneurosome preparation from guinea pig cerebral cortex: cyclic adenosine 3′5′-monophosphate-generating systems, receptors and enzymes. *J. Neurosci.* 5: 2240–2253, 1985.
323. HOLLINGSWORTH, E. B., E. B. SEARS, AND J. W. DALY. An activator of protein kinase C (phorbol-12-myristate-13-acetate) augments 2-chloroadenosine elicited accumulation of cyclic AMP in guinea pig cerebral cortical particulate preparations. *FEBS Lett.* 184: 339–342, 1985.
324. HONEGGER, C. G., L. M. KREPELKA, V. STEINMAN, AND H. P. VON HAHN. Distribution of ^{3}H and ^{14}C-labeled potential neurotransmitters on a discontinuous density gradient after uptake into rat cerebral cortex slices. *Eur. Neurol.* 12: 236–252, 1974.
325. HÖSLI, L., AND E. HÖSLI. Electrophysiologic and autoradiographic evidence for receptors for biogenic amines on astrocytes in explant cultures of rat CNS. In: *Glial Cell Receptors*, edited by H. K. Kimelberg. New York: Raven, 1988, p. 77–93.
326. HÖSLI, L., E. HÖSLI, U. SCHNEIDER, AND W. WIGET. Evidence for the existence of histamine H_1- and H_2-receptors on astrocytes of cultured rat central nervous system. *Neurosci. Lett.* 48: 287–291, 1984.
327. HOUGH, L. B. Barbiturate-induced inhibition of rat brain histamine turnover. *Biochem. Pharmacol.* 36: 3321–3323, 1987.
328. HOUGH, L. B. Cellular localization and possible functions for brain histamine: recent progress. *Prog. Neurobiol. Oxf.* 30: 469–505, 1988.
328a. ICHINOSE, M., AND P. J. BARNES. Inhibitory histamine H_2-receptors on cholinergic nerves in human airways. *Eur. J. Pharmacol.* 163: 383–386, 1989.
328b. ICHINOSE, M. AND P. J. BARNES. Histamine H_2-receptors modulate nonadrenergic noncholinergic bronchoconstriction in guinea-pig in vivo. *Eur. J. Pharmacol.* 174: 49–56, 1989.
328c. ICHINOSE, M., M. G. BELVISI, AND P. J. BARNES. Histamine H_2-receptors inhibit neurogenic microvascular leakage in airways. *J. Appl. Physiol.* 68: 21–25, 1990.
329. HOUGH, L. B., AND E. F. DOMINO. *tele*-Methylhistamine oxidation by type B monoamine oxidase. *J. Pharmacol. Exp. Ther.* 208: 422–425, 1979.
330. HOUGH, L. B., AND E. F. DOMINO. *tele*-Methylhistamine distribution in rat brain. *J. Neurochem.* 32: 1865–1866, 1979.
331. HOUGH, L. B., S. D. GLICK, AND K. SU. A role for histamine and histamine H_2-receptors in non-opiate footshock-induced analgesia. *Life Sci.* 36: 859–866, 1985.
332. HOUGH, L. B., R. C. GOLDSCHMIDT, S. D. GLICK, AND J. PADAWER. Mast cells in rat brain: characterization, localization and histamine content. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 131–142.
333. HOUGH, L. B., AND J. P. GREEN. Histamine-activated adenylate cyclase in brain homogenates of several species. *Brain Res.* 219: 363–370, 1981.
334. HOUGH, L. B., AND J. P. GREEN. Histamine and its receptors in the nervous system. In: *Handbook of Neurochemistry. Receptors in the Nervous System* (2nd ed.), edited by A. Lajtha. New York: Plenum, 1984, vol. 6, p. 145–211.
335. HOUGH, L. B., J. K. KHANDELWAI, R. C. GOLDSCHMIDT, M. DIOMANDE, AND S. D. GLICK. Normal levels of histamine and *tele*-methylhistamine in mast cell-deficient mouse brain. *Brain Res.* 292: 139–138, 1984.
336. HOUGH, L. B., J. K. KHANDELWAI, AND J. P. GREEN. Ontogeny of subcellular distribution of rat brain *tele*-methylhistamine. *J. Neurochem.* 38: 1593–1599, 1982.
337. HOUGH, L. B., J. K. KHANDELWAI, AND J. P. GREEN. Effect of pargyline on *tele*-methylhistamine and histamine in rat brain. *Biochem. Pharmacol.* 31: 4074–4076, 1982.
338. HOUGH, L. B., J. K. KHANDELWAI, AND J. P. GREEN. Histamine turnover in regions of rat brain. *Brain Res.* 291: 103–109, 1984.
339. HOUGH, L. B., J. K. KHANDELWAI, AND J. P. GREEN. Inhibition of brain histamine metabolism by metoprine. *Biochem. Pharmacol.* 35: 307–310, 1986.
340. HOUGH, L. B., K. L. SU, R. C. GOLDSCHMIDT, J. K. KHANDELWAI, M. V. NEWTON, AND S. D. GLICK. No evidence for histamine-mediated morphine analgesia. *Neuropharmacology* 23: 705–709, 1984.
341. HUANG, M., AND G. I. DRUMMOND. Adenylate cyclase in cerebral microvessels: action of guanine nucleotides, adenosine and other agonists. *Mol. Pharmacol.* 16: 462–472, 1979.
342. IBRAHIM, M. Z. M. The immediate and delayed effects of compound 48/80 on mast cells and parenchyma of rabbit brain. *Brain Res.* 17: 348–360, 1970.
343. IBRAHIM, M. Z. M. The mast cells of the mammalian central nervous system. I. Morphology, distribution and histochemistry. *J. Neurol. Sci.* 21: 431–478, 1974.
344. IBRAHIM, M. Z. M. The mast cells of the mammalian central nervous system. II. The effect of proton irradiation in the monkey. *J. Neurol. Sci.* 21: 479–496, 1974.
345. IBRAHIM, M. Z. M. Glycogen and its related enzymes of metabolism in the central nervous system. *Adv. Anat. Embryol. Cell Biol.* 52: 1–85, 1975.
346. IBRAHIM, M. Z. M., M. E. AL-WIRR, AND N. BAHUTH. The mast cells of the mammalian central nervous system. III. Ultra

structural characteristics in the adult rat brain. *Acta Anat.* 104: 134–154, 1979.

347. IBRAHIM, M. Z. M., V. TENEKJIAN, AND M. A. A. UTHMAN. The effect of compound 48/80 on the perivascular granular cells (neurolipomastocytes) of the rabbit brain. *Anat. Rec.* 104: 434, 1979.

348. IBRAHIM, M. Z. M., M. A. A. UTHMAN, V. TENEKJIAN, AND T. WIEDMAN. The mast cells of the mammalian central nervous system. V. The effect of compound 48/80 on the neurolipomastoid cells and related areas of the CNS: early changes. *Cell Tissue Res.* 212: 99–116, 1980.

348a. ICHINOSE, M., AND P. J. BARNES. Inhibitory histamine H_3-receptors on cholinergic nerves in human airways. *Eur. J. Pharmacol.* 163: 333–336, 1989.

348b. ICHINOSE, M., AND P. J. BARNES. Histamine H_3-receptors modulate nonadrenergic noncholinergic bronchoconstriction in guinea-pig in vivo. *Eur. J. Pharmacol.* 174: 49–56, 1989.

348c. ICHINOSE, M., M. G. BELVISI, AND P. J. BARNES. Histamine H_3-receptors inhibit neurogenic microvascular leakage in airways. *J. Appl. Physiol.* 68: 21–25, 1990.

349. ICHINOSE, M., C. D. STRETTON, J. C. SCHWARTZ, AND P. J. BARNES. Histamine H_3-receptors inhibit cholinergic neurotransmission in guinea pig airways. *Br. J. Pharmacol.* 97: 13–15, 1989.

350. INAGAKI, N., A. YAMATODANI, M. ANDO-YAMAMOTO, M. TOHYAMA, T. WATANABE, AND H. WADA. Organisation of histaminergic fibers in rat brain. *J. Comp. Neurol.* 273: 283–300, 1988.

351. INAGAKI, N., A. YAMATODANI, K. SHINODA, P. PANULA, T. WATANABE, Y. SHIOTANI, AND H. WADA. Histaminergic nerve fibers in the median eminence and hypophysis of rats demonstrated immunocytochemically with antibodies against histidine decarboxylase and histamine. *Brain Res.* 439: 402–405, 1988.

352. INAGAKI, N., A. YAMATODANI, K. SHINODA, Y. SHIOTANI, M. TOHYAMA, T. WATANABE, AND H. WADA. The histaminergic innervation of the mesencephalic nucleus of the trigeminal nerve in rat brain: a light and electron microscopical study. *Brain Res.* 418: 388–391, 1987.

353. IRVINE, R. F., A. J. LETCHER, AND R. M. C. DAWSON. Phosphatidylinositol-4,5-biphosphate phosphodiesterase and phosphomonoesterase activities of rat brain. *Biochem. J.* 218: 177–185, 1984.

354. ISHIKAWA, S., AND N. SPERELAKIS. A novel class (H_2) of histamine receptors on perivascular nerve terminals. *Nature Lond.* 327: 158–160, 1987.

355. ITOH, Y., M. NISHIBORI, R. OISHI, AND K. SAEKI. Neuronal histamine inhibits metamphetamine-induced locomotor hyperactivity in mice. *Neurosci. Lett.* 43: 305–309, 1984.

356. ITOH, Y., M. NISHIBORI, R. OISHI, AND K. SAEKI. Changes in histamine metabolism in the mouse hypothalamus induced by acute administration of ethanol. *J. Neurochem.* 45: 1880–1885, 1985.

357. ITOH, Y., R. OISHI, M. NISHIBORI, AND K. SAEKI. Phencyclidine and the dynamics of mouse brain histamine. *J. Pharmacol. Exp. Ther.* 235: 788–792, 1985.

358. ITOH, Y., R. OISHI, M. NISHIBORI, AND K. SAEKI. Comparison of effects of phencyclidine and methamphetamine on body temperature in mice: a possible role for histamine neurons in thermoregulation. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 322: 293–296, 1986.

359. ITOH, Y., R. OISHI, M. NISHIBORI, AND K. SAEKI. Involvement of opioid receptors in phencyclidine-induced enhancement of brain histamine turnover in mice. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 335: 285–289, 1987.

360. ITOH, Y., R. OISHI, M. NISHIBORI, AND K. SAEKI. Involvement of Mu receptors in the opioid-induced increase in the turnover of mouse brain histamine. *J. Pharmacol. Exp. Ther.* 244: 1021–1026, 1988.

361. JAFFERJI, S. S., AND R. H. MICHELL. Stimulation of phosphatidylinositol turnover by histamine, 5-hydroxytryptamine and adrenaline in the longitudinal smooth muscle of guinea pig ileum. *Biochem. Pharmacol.* 25: 1429–1430, 1976.

362. JARROTT, B., J. T. HJELLE, AND S. SPECTOR. Association of histamine with cerebral microvessels in regions of bovine brain. *Brain. Res.* 168: 329–330, 1979.

363. JOHNSON, C. L. Histamine receptors and cyclic nucleotides. In: *Pharmacology of Histamine Receptors*, edited by C. R. Ganellin and M. E. Parsons. Bristol, UK: Wright, 1982, p. 146–216.

364. JOHNSON, C. L., AND D. G. SAWUTZ. Desensitization of histamine H_2 receptors in human leukemia cells. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 79–88.

365. JONES, B. C., K. BEAUMONT, R. E. HRUSKA, G. J. WASTEK, AND H. I. YAMAMURA. L-Histidine: high affinity transport into rat synaptosomes. *Proc. West. Pharmacol. Soc.* 18: 157–159, 1976.

366. JONES, H., P. B. BRADLEY, AND F. ROBERTS. Histamine-induced excitation of spontaneously active medullary neurones in the rat brain is mediated by H_2-receptors. *Neuropharmacology* 24: 1231–1239, 1985.

367. JOO, F., Z. RAKONCZAY, AND M. WOLLEMANN. cAMP-mediated regulation of the permeability in brain capillaries. *Experientia Basel* 31: 582–584, 1975.

367a. JOSEPH, D. R., P. M. SULLIVAN, Y. M. WANG, C. KOZAK, D. A. FENSTERMACHER, M. E. BEHRENDSEN, AND C. A. ZAHNOW. Characterization and expression of the complementary DNA encoding rat histidine decarboxylase. *Proc. Natl. Acad. Sci. USA 87*: 733–737, 1990.

368. JOSEPH-BRAVO, P., J. L. CHARLI, J. M. PALACIOS, AND C. KORDON. Effect of neurotransmitters on the in vitro release of immunoreactive thyrotropin-releasing hormone from rat median basal hypothalamus. *Endocrinology* 104: 801–806, 1979.

369. JOUVET, M., K. SAKAI, AND J. S. LIN. Role of histaminergic neurons in the regulation of arousal in the cat (abstract). *Eur. J. Neurosci., Suppl.* : 5, 1988.

370. KAHLSON, G., AND E. ROSENGREN. New approaches to the physiology of histamine. *Physiol. Rev.* 48: 155–196, 1968.

371. KAKIUCHI, S., AND T. W. RALL. The influence of chemical agents on the accumulation of adenosine 3′-5′ monophosphate in slices of rabbit cerebellum. *Mol. Pharmacol.* 4: 367–378, 1968.

372. KAKUCSKA, I., AND G. B. MAKARA. Various putative neurotransmitters affect growth hormone (GH) release in rats with anterolateral hypothalamic deafferentation of the medial basal hypothalamus: evidence for mediation by a GH-releasing factor. *Endocrinology* 123: 318–323, 1988.

373. KALIVAS, P. W. Histamine induced arousal in the conscious and pentobarbital-pretreated rat. *J. Pharmacol. Exp. Ther.* 222: 37–42, 1982.

374. KANBA, S., AND E. RICHELSON. Antidepressants are weak competitive antagonists of histamine H_1 receptors in dissociated brain tissue. *Eur. J. Pharmacol.* 94: 313–318, 1983.

375. KANBA, S., AND E. RICHELSON. Histamine H_2 receptors in human brain labelled with [^{3}H] doxepin. *Brain Res.* 304: 1–7, 1984.

376. KANDASAMY, S. B., AND W. A. HUNT. Involvement of histamine H_1 and H_2 receptors in hypothermia induced by ionizing radiation in guinea pigs. *Life Sci.* 42: 555–563, 1987.

377. KANDEL, S. I., G. H. STEINBERG, J. W. WELLS, M. KANDEL, AND G. GORNALL. Separate binding sites for histaminic drugs in rat cerebral cortex. *Biochem. Pharmacol.* 29: 2269–2272, 1980.

378. KANOF, P. D., AND P. GREENGARD. Brain histamine receptors as targets for antidepressant drugs. *Nature Lond.* 272: 329–333, 1978.

379. KANOF, P. D., L. R. HEGSTRAND, AND P. GREENGARD. Biochemical characterization of histamine-sensitive adenylate cyclase in mammalian brain. *Arch. Biochem. Biophys.* 182: 321–334, 1977.

380. KARBON, E. W., AND S. J. ENNA. Characterization of the relationship between γ-aminobutyric acid B agonists and transmitter-coupled cyclic nucleotide-generating systems in rat brain. *Mol. Pharmacol.* 27: 53–59, 1984.

381. KARNUSHINA, I. L., J. M. PALACIOS, G. BARBIN, E. DUX, F. JOO, AND J. C. SCHWARTZ. Histamine-related enzymes and histamine receptors in isolated brain capillaries. *Agents Actions* 9: 89–90, 1979.

382. KARNUSHINA, I. L., J. M. PALACIOS, G. BARBIN, E. DUX, F. JOO, AND J. C. SCHWARTZ. Studies on a capillary-rich fraction isolated from brain: histaminic components and characterization

of the histamine receptors linked to adenylate cyclase. *J. Neurochem.* 34: 1201–1208, 1980.
388. KATAOKA, K., AND E. DE ROBERTIS. Histamine in isolated small nerve endings and synaptic vesicles of rat brain cortex. *J. Pharmacol. Exp. Ther.* 156: 114–125, 1967.
384. KENDALL, D. A., J. W. PERKANY, AND S. J. ENNA. Properties of ^{3}H-cimetidine binding in rat brain membrane fractions. *Life Sci.* 26: 1293–1302, 1980.
385. KENDALL, D. A., AND S. J. HILL. Adenosine inhibition of histamine-stimulated inositol phospholipid hydrolysis in mouse cerebral cortex. *J. Neurochem.* 50: 497–502, 1988.
386. KENDALL, D. A., AND S. R. NAHORSKI. Inositol phospholipid hydrolysis in rat cerebral cortical slices. II. Calcium requirement. *J. Neurochem.* 42: 1388–1394, 1984.
387. KHANDELWAL, J. K., L. B. HOUGH, AND J. P. GREEN. Regional distribution of the histamine metabolite, *tele*-methylimidazoleacetic acid, in rat brain: effects of pargyline and probenecid. *J. Neurochem.* 42: 519–522, 1984.
388. KHANDELWAL, J. K., L. B. HOUGH, A. M. MORRISHOW, AND J. P. GREEN. Measurement of *tele*-methylhistamine and histamine in human cerebrospinal fluid, urine, and plasma. *Agents Actions* 12: 583–590, 1982.
389. KHANDELWAL, J. K., L. B. HOUGH, B. PAZHENCHEVSKY, A. M. MORRISHOW, AND J. P. GREEN. Presence and measurement of methyl-imidazoleacetic acid in brain and body fluids. *J. Biol. Chem.* 257: 12815–12819, 1982.
390. KIERNAN, J. A. A comparative survey of the mast cells of the mammalian brain. *J. Anat.* 121: 303–311, 1976.
391. KIRSTEN, E. B., AND J. N. SHARMA. Microiontophoresis of acetylcholine, histamine and their antagonists on neurones in the medial and lateral vestibular nuclei of the cat. *Neuropharmacology* 15: 743–753, 1976.
392. KISHIMOTO, S., H. KIMURA, AND T. MAEDA. Histochemical demonstration for monoamine oxidase (MAO) by a new coupled peroxidation method. *Cell Mol. Biol.* 29: 61–69, 1982.
393. KITAHAMA, K., K. SAKAI, H. TAGO, H. KIMURA, T. MAEDA, AND M. JOUVET. Monoamine oxidase-containing neurons in the cat hypothalamus: distribution and ascending projection to the cerebral cortex. *Brain Res.* 224: 155–159, 1984.
394. KIYONO, S., M. SEO, M. SHIBAGAKI, T. WATANABE, K. MAEYAMA, AND H. WADA. Effects of diphenhydramine, histamine H_2-receptor antagonist, on rat sleep-waking parameters. *Neurosciences* 10: 241–248, 1984.
396. KIYONO, S., M. L. SEO, M. SHIBAGAKI, T. WATANARE, K. MAEYAMA, AND H. WADA. Effects of α-fluoromethylhistidine on sleep-waking parameters in rats. *Physiol. Behav.* 34: 615–617, 1985.
396. KLEIN, M. G., AND S. B. GERTNER. Evidence for a role of endogenous histamine in central cardiovascular regulation: inhibition of histamine-*N*-methyltransferase by SKF 91488. *J. Pharmacol. Exp. Ther.* 216: 315–320, 1981.
397. KLEIN, M. G., AND S. B. GERTNER. Studies of the mechanism of the cardiovascular action of central injections of histamine. *Neuropharmacology* 22: 1109–1115, 1983.
398. KLEIN, I., AND G. S. LEVEY. Activation of myocardial adenyl cyclase by histamine in guinea-pig, cat and human heart. *J. Clin. Invest.* 50: 1012–1015, 1971.
399. KNIGGE, U., F. W. BACH, S. MATZEN, P. BANG, AND J. WARBERG. Effects of histamine on the secretion of pro-opiomelanocortin derived peptides in rats. *Acta Endocrinol.* 119: 312–319, 1988.
400. KNIGGE, U., A. DEJGAARD, F. WOLLESEN, B. THUESEN, AND P. M. CHRISTIANSEN. Histamine regulation of prolactin secretion through H_1- and H_2-receptors. *J. Clin. Endocrinol. Metab.* 55: 118–122, 1982.
401. KNIGGE, U., S. MATZEN, AND J. WARBERG. Histaminergic stimulation of prolactin secretion mediated via H_1- or H_2-receptors: dependence on routes of administration. *Neuroendocrinology* 44: 41–48, 1986.
402. KNIGGE, U., S. MATZEN, AND J. WARBERG. Effects of H_2-receptor antagonists on prolactin secretion: specificity and mediation of the response. *Acta Endocrinol.* 115: 461–468, 1987.
403. KNIGGE, U., S. MATZEN, AND J. WARBERG. Histaminergic mediation of the stress-induced release of prolactin in male rats. *Neuroendocrinology* 47: 68–74, 1988.
404. KNIGGE, U., S. MATZEN, AND J. WARBERG. Histaminergic regulation of prolactin secretion: involvement and tuberoinfundibular dopaminergic neurons. *Neuroendocrinology* 48: 167–173, 1988.
405. KNIGGE, U., I. SLEIMANN, S. MATZEN, AND J. WARBERG. Histaminergic regulation of prolactin secretion: involvement of serotoninergic neurons. *Neuroendocrinology* 48: 527–533, 1988.
406. KNIGGE, U., B. THUESEN, AND P. M. CHRISTIANSEN. Histaminergic regulation of prolactin secretion: dose-response relationship and possible involvement of the dopaminergic system. *J. Clin. Endocrinol. Metab.* 62: 491–496, 1986.
407. KNIGGE, U., F. WOLLESEN, A. DEJGAARD, B. THUESEN, AND P. M. CHRISTIANSEN. Comparison between dose-responses of prolactin, thyroid stimulating hormone, and growth hormone to two different histamine H_2-receptor antagonists in normal men. *Clin. Endocrinol.* 15: 585–592, 1981.
408. KOBAYASHI, R. M., AND I. J. KOPIN. The effects of stress and environmental lighting on histamine in the rat brain. *Brain Res.* 74: 356–359, 1974.
409. KODAMA, T., Y. MATSUKADO, AND H. SHIMIZA. The cAMP system of human brain. *Brain Res.* 50: 135–146, 1973.
410. KÖHLER, C., H. ERICSON, T. WATANABE, J. POLAK, S. L. PALAY, Y. PALAY, AND V. CHAN-PALAY. Galanin immunoreactivity in hypothalamic histaminergic neurons: further evidence for multiple chemical messengers in the tuberomammillary nucleus. *J. Comp. Neurol.* 250: 58–64, 1986.
411. KÖHLER, C., C. W. SWANSON, L. HAGLUND, AND J. YEN WU. The cytoarchitectura, histochemistry and projections of the tuberomammillary nucleus in the rat. *Neuroscience* 16: 85–110, 1985.
412. KOLLONITSCH, J., A. A. PATCHETT, S. MARBURG, A. L. MAYCOCK, L. M. PERKINS, G. A. DOLDOURAS, D. E. DUGGAN, AND S. D. ASTER. Selective inhibitors of biosynthesis of aminergic neurotransmitters. *Nature Lond.* 274: 906–908, 1978.
413. KONISHI, H., AND Y. KAKIMOTO. Formation of γ-glutamylhistamine from histamine in rat brain. *J. Neurochem.* 27: 1461–1463, 1976.
414. KÖRNER, M., M. L. BOUTHENET, C. R. GANELLIN, M. GARBARG, C. GROS, R. J. IFE, N. SALES, AND J. C. SCHWARTZ. [^{125}I]iodobolpyramine, a highly sensitive probe for histamine H_1-receptors in guinea-pig brain. *Eur. J. Pharmacol.* 120: 151–160, 1986.
415. KRALY, F. S. Histamine: a role in normal drinking. *Appetite* 6: 153–158, 1985.
416. KRALY, F. S., AND K. R. JUNE. A vagally mediated histaminergic component of food-related drinking in the rat. *J. Comp. Physiol. Psychol.* 1: 89–104, 1982.
417. KRALY, F. S., AND S. M. SPECHT. Histamine plays a major role for drinking elicited by spontaneous eating in rats. *Physiol. Behav.* 33: 611–614, 1984.
418. KRISHNAMOORTHY, K. M., M. GARBARG, J. FEGER, AND J. C. SCHWARTZ. Augmentation in hypothalamic histamine induced by diencephalic lesions in rats. *Agents Actions* 3: 181, 1973.
419. KRÜGER, P. G. Demonstration of mast cells in the albino rat brain. *Experientia Basel* 20: 310–311, 1974.
420. KUBO, N., O. SHIRAKAWA, T. KUNO, AND C. TANAKA. Antimuscarinic effects of antihistamines: quantitative evaluation by receptor-binding assay. *Jpn. J. Pharmacol.* 43: 277–282, 1987.
421. KUBOTA, H., H. HAYASHI, T. WATANABE, Y TAGUCHI, AND H. WADA. Mechanism of inactivation of mammalian L-histidine decarboxylase by (*S*)-α-fluoromethylhistidine. *Biochem. Pharmacol.* 33: 983–990, 1984.
422. KUHAR, M. J. The mismatch problem in receptor mapping studies. *Trends Neurosci.* 8: 190–191, 1985.
423. KUHAR, M. J., K. M. TAYLOR, AND S. H. SNYDER. The subcellular localization of histamine and histamine methyl-transferase in rat brain. *J. Neurochem.* 18: 1515–1527, 1971.
424. KUNO, T., N. KUBO, AND C. TANAKA. Molecular size of histamine H_1 receptor determined by target size analysis. *Biochem. Biophys. Res. Commun.* 129: 639–644, 1985.
425. KUO, J. F., T. P. LEE, P. L. REYES, K. G. WALTON, T. E. DON-

NELLY, AND P. GREENGARD. Cyclic nucleotide-dependent protein kinases. X. An assay method for the measurement of guanosine 3',5'-monophosphate in various biological materials and a study of agents regulating its levels in heart and brain. *J. Biol. Chem.* 247: 16–22, 1972.

426. KWIATKOWSKI, H. Histamine in nervous tissues. *J. Physiol. Lond.* 102: 32–41, 1943.

427. LAKOSKI, J. M., AND G. K. AGHAJANIAN. Effects of histamine, H_1- and H_2-receptor antagonists on the activity of serotonergic neurons in the dorsal raphe nucleus. *J. Pharmacol. Exp. Ther.* 227: 517–523. 1983.

428. LAKOSKI, J. M., D. W. GALLAGER, AND G. K. AGHAJANIAN. Histamine-induced depression of serotonergic dorsal raphe neurons: antagonism by cimetidine: a reevaluation. *Eur. J. Pharmacol.* 103: 153–158, 1984.

429. LE FUR, G., C. MALGOURIS, AND A. UZAN. Effect of mequitazine, a non sedative antihistamine on brain H_1 receptors. *Life Sci.* 29: 547–552, 1981.

430. LEIBOWITZ, S. F. Histamine: a stimulatory effect on drinking behavior in the rat. *Brain Res.* 63: 440–444, 1973.

431. LEIBOWITZ, S. F. Histamine: modification of behavioral and physiological components of body fluid homeostasis. In: *Histamine Receptors*, edited by T. O. Yellin. New York: Spectrum, 1979, p. 219–254.

432. LEVEY, G. S., AND I. KLEIN. Solubilized myocardial adenylate cyclase. Restoration of histamine responsiveness by phosphatidylserine. *J. Clin. Invest.* 51: 1578–1582, 1972.

433. LEVINE, R. J., T. L. SATO, AND A. SJOERDSMA. Inhibition of histamine synthesis in the rat by alpha-hydrazino analog of histidine and 4-bromo-3-hydroxybenzyloxyamine. *Biochem. Pharmacol* 14: 139–149, 1965.

434. LEWIS, J. W., G. W. TERMAN, L. R. NELSON, AND J. C. LIEBESKIND. Opioid and non-opioid stress analgesia. In: *Stress-Induced Analgesia*, edited by M. D. Trickebank and G. Curzon. Chichester, UK: Wiley, 1984, p. 103–133.

435. LIBERTUN, C., AND S. M. MCCANN. The possible role of histamine in the control of prolactin and gonadotropin release. *Neuroendocrinology* 20: 110–120, 1976.

436. LIN, J. S., K. SAKAI, AND M. JOUVET. Rôle des systèmes histaminergiques hypothalamiques dans la régulation des états de vigilance chez le chat. *C. R. Hebd. Seances Acad. Sci.* 303: 469–474, 1986.

437. LIN, J. S., K. SAKAI, AND M. JOUVET. Evidence for histaminergic arousal mechanisms in the hypothalamus of cat. *Neuropharmacology* 27: 111–122, 1988.

437a. LIN, J. S., K. SAKAI, G. VANNI-MERCIER, J. M. ARRANG, M. GARBARG, J. C. SCHWARTZ, AND M. JOUVET. Involvement of histamine in arousal mechanisms demonstrated with H_3-receptor ligands in the cat. *Brain Res.* In press.

438. LINDAHL, K. M. The histamine methylating enzyme system in liver. *Acta Physiol. Scand.* 49: 114–138, 1960.

439. LIOU, S. Y., S. SHIBATA, K. YAMAKAWA, AND S. UEKI. Inhibitory and excitatory effects of histamine on suprachiasmatic neurons in rat hypothalamic slice preparation. *Neurosci. Lett.* 41: 109–113, 1983.

440. LIPINSKI, J. F., H. H. SCHAUMBURG, AND R. J. BALDESSARINI. Regional distribution of histamine in human brain. *Brain Res.* 52: 403–408, 1973.

441. LOMAX, P., AND M. D. GREEN. Histamine and temperature regulation. In: *Temperature Regulation and Drug Action*, edited by P. Lomax, E. Schonbaum, and J. Jacob. Basel: Karger, 1975, p. 85–93.

442. MAAYANI, S., L. B. HOUGH, H. WEINSTEIN, AND J. P. GREEN. Response of the histamine H_2-receptor in brain to antidepressant drugs. In: *Advances in Biochemistry Psychopharmacology. Typical and Atypical Antidepressants*, edited by G. Racagni and E. Costa. New York: Raven, 1982, vol. 31, p. 133–147.

443. MAEDA, K., AND L. A. FROHMAN. Dissociation of systemic and central effects of neurotensin on the secretion of growth hormone, prolactin and thyrotropin. *Endocrinology* 103: 1903–1909, 1978.

444. MAEDA, T., H. IMAI, AND H. KIMURA. Electron microscopic localization of monoamine oxidase in rat brain. *Neurosci. Lett. Suppl.* 13: 70, 1983.

445. MAEDA, T., H. KIMURA, T. NAGAI, H. IMAI, R. ARAI, T. SAKUMOTO, K. SAKAI, K. KITAHAMA, AND M. JOUVET. Histochemistry of the magnocellular neurons in the posterior hypothalamus with special reference to MAO activity and ability of 5-HTP uptake and decarboxylation. *Acta Histochem. Cytochem.* 17: 179–193, 1984.

446. MAEYAMA, K., T. WATANABE, Y. TAGUCHI, A. YAMATODANI, AND H. WADA. The effect of α-fluoromethylhistidine, a suicide inhibitor of histidine decarboxylase, on histamine levels in mouse tissues. *Biochem. Pharmacol.* 31: 2367–2370, 1982.

447. MAEYAMA, K., T. WATANABE, A. YAMATODANI, Y. TAGUCHI, H. KAMBE, AND H. WADA. Effect of α-fluoromethylhistidine on the histamine content of the brain of W/W^v mice devoid of mast cells: turnover of brain histamine. *J. Neurochem.* 41: 128–134, 1983.

448. MAGISTRETTI, P. J., J. H. MORRISSON, W. J. SHOEMAKER, V. SAPIN, AND F. E. BLOOM. Vasoactive intestinal polypeptide induces glycogenolysis in mouse cortical slices: a possible regulatory mechanism for the local control of energy metabolism. *Proc. Natl. Acad. Sci. USA* 78: 6535–6539, 1981.

449. MAGISTRETTI, P. J., AND M. SCHORDERET. Norepinephrine and histamine potentiate the increases in cyclic adenosine 3',5'-monophosphate elicited by vasoactive intestinal polypeptide in mouse cerebral cortical slices: mediation by α_1-adrenergic and H_1 histaminergic receptors. *J. Neurosci.* 5: 362–368, 1985.

450. MALICK, J. B. The pharmacology of isolation-induced aggressive behavior in mice. In: *Current Developments in Psychopharmacology*, edited by W. B. Essman and L. Valzelli. New York: SP, 1979, vol. 5, p. 1–27.

451. MALINOWSKA, D. H., G. SACHS, AND J. CUPPOLETTI. Gastric H^+ secretion: histamine (cAMP-mediated) activation of protein phosphorylation. *Biochim. Biophys. Acta* 972: 95–109, 1988.

452. MANDELBROD, I., S. FELDMAN, AND R. WERMAN. The effects of iontophoretic application of putative neurotransmitters on the electrical activity of rat medial basal hypothalamic neurons in relation to their steroid sensitivity. *Brain Res.* 272: 115–127, 1983.

453. MARTIN, J. R., M. C. BEINFELD, AND T. C. WESTFALL. Blood pressure increases after injection of neuropeptide Y into posterior hypothalamic nucleus. *Am. J. Physiol.* 254 (*Heart Circ. Physiol.* 23): H979–H986, 1988.

454. MARTIN, S. A. M., AND J. O. BISHOP. Purification and characterization of histidine decarboxylase from mouse kidney. *Biochem. J.* 234: 349–354, 1986.

455. MARTIN, S. A. M., AND G. BULFIELD. A regulatory locus, Hdc-e determines the response of mouse kidney histidine decarboxylase to estrogen. *Biochem. Genet.* 22: 1037–1046, 1984.

456. MARTIN, S. A. M., AND G. BULFIELD. A structural gene (Hdc-s) for mouse kidney histidine decarboxylase. *Biochem. Genet.* 22: 645–656, 1984.

456a. MARTINEZ-MIR, M. I., H. POLLARD, J. MOREAU, J. M. ARRANG, M. RUAT, E. TRAIFFORT, J. C. SCHWARTZ, AND J. M. PALACIOS. Three histamine receptors (H_1, H_2, and H_3) visualized in the brain of human and non human primates. *Brain Res.* In press.

457. MARTRES, M. P., M. BAUDRY, AND J. C. SCHWARTZ. Histamine synthesis in the developing rat brain: evidence for a multiple compartmentation. *Brain Res.* 83: 261–276, 1975.

458. MARWAHA, J., B. J. HOFFER, AND R. FREEDMAN. Electrophysiologic evidence for histamine receptors in rat cerebellum. *Exp. Neurol.* 74: 285–292, 1981.

459. MATSUMOTO, T., H. KANAIDE, J. NISHIMURA, Y. SHOGAKIUCHI, S. KOBAYASHI, AND M. NAKAMURA. Histamine activates H_1-receptors to induce cytosolic free calcium transients in cultured vascular smooth muscle cells from rat aorta. *Biochem. Biophys. Res. Commun.* 135: 172–177, 1986.

460. MATUSZEWSKA, B., AND R. T. BORCHARDT. Guinea pig brain histamine *N*-methyltransferase: purification and partial characterization. *J. Neurochem.* 41: 113–118, 1983.

461. MAZURKIEWICZ-KWILECKI, I. M. Single and repeated air

blast stress and brain histamine. *Pharmacol. Biochem. Behav.* 12: 35–39, 1980.
462. MAZURKIEWICZ-KWILECKI, I. M. Brain histamine plasma corticosterone interactions. *Life Sci.* 32: 1099–1106, 1983.
463. MAZURKIEWICZ-KWILECKI, I. M., AND B. BIELKIEWICZ. Effect of diphenhydramine on stress-induced changes in brain histidine decarboxylase activity, histamine and plasma corticosterone levels. *Pharmacol. Biochem. Behav.* 16: 591–597, 1982.
464. MCGINTY, D. J. Somnolence, recovery and hyposomnia following ventromedial diencephalic lesion in the rat. *Electroencephalogr. Clin. Neurophysiol.* 26: 70–79, 1969.
465. MCNEILL, J. H., AND L. D. MUSCHEK. Histamine effects on cardiac contractility, phosphorylase and adenyl cyclase. *J. Mol. Cell. Cardiol.* 4: 611–624, 1972.
466. MELANDER, T., T. HÖKFELT, AND A. RÖKAEUS. Distribution of galanin like immunoreactivity in the rat central nervous system. *J. Comp. Neurol.* 248: 475–517, 1986.
467. MICHAELSON, I. A., AND P. Z. COFFMAN. The subcellular localization of histamine in guinea pig brain—a re-evaluation. *Biochem. Pharmacol.* 16: 2085–2090, 1967.
468. MICHELL, R. H. Inositol phospholipids and cell surface receptor function. *Biochim. Biophys. Acta* 415: 81–147, 1975.
469. MIRRO, R., D. W. BUSIJA, W. M. ARMSTEAD, AND C. W. LEFFLER. Histamine dilates pial arterioles of newborn pigs through prostanoid production. *Am. J. Physiol.* 254 (*Heart Circ. Physiol.* 23): H1023–H1026, 1988.
470. MIYAKE, A., S. OHTSUKA, T. NISHIZAKI, K. TASAKA, T. AONO, O. TANIZAWA, A. YAMATODANI, T. WATANABE, AND H. WADA. Involvement of H_1 histamine receptor in basal and estrogen-stimulated luteinizing hormone-releasing hormone secretion in rats in vitro. *Neuroendocrinology* 45: 191–196, 1987.
471. MONNIER, M., R. SAUER, AND A. M. HATT. The activating effect of histamine on the central nervous system. *Int. Rev. Neurobiol.* 12: 265–305, 1970.
472. MONTI, J. M., T. PELLEJERO, AND H. JANTOS. Effects of H_1 and H_2 histamine receptor agonists and antagonists on sleep and wakefulness in the rat. *J. Neural Transm.* 66: 1–11, 1986.
473. MONTI, J. M., T. PELLEJERO, H. JANTOS, AND S. PAZOS. Role of histamine in the control of sleep and waking. In: *Sleep: Neurotransmitters and Neuromodulators*, edited by A. Wauquier. New York: Raven, 1985, p. 197–209.
474. MORGAN, L. O. Cell groups in the tuber cinereum of the dog. *J. Comp. Neurol.* 51: 271–297, 1930.
475. MULDER, A. H., R. P. J. M. SMITS, AND H. W. M. STEINBUSCH. Neuronal uptake and release of histamine in the central nervous system. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 155–162.
476. MULDER, A. H., R. G. M. VAN AMSTERDAM, M. WILBRINK, AND A. N. M. SCHOFFELMEER. Release of ^{3}H-histamine from rat brain slices by potassium depolarization, electrical stimulation, and veratrine: evidence for uptake and release of histamine by neurons. *Neurochem. Int.* 5: 291–297, 1983.
477. NAGY, J. I., J. D. GEIGER, AND P. E. DADDONA. Adenosine uptake site in rat brain: identification using [^{3}H]-nitrobenzylthioinosine and colocalization with adenosine deaminase. *Neurosci. Lett.* 55: 47–53, 1985.
478. NAGY, J. I., A. A. LABELLA, M. BUSS, AND P. E. DADDONA. Immunohistochemistry of adenosine deaminase: implications for adenosine neurotransmission. *Science Wash. DC* 224: 166–168, 1984.
479. NAHORSKI, S. R., AND K. J. ROGERS. The role of catecholamines in the action of amphetamine and l-DOPA on cerebral energy metabolism. *Neuropharmacology* 14: 283–290, 1975.
480. NAHORSKI, S. R., K. J. ROGERS, AND C. EDWARDS. Cerebral glycogenolysis and stimulation of β-adrenoreceptors and histamine H_2-receptors. *Brain Res.* 92: 529–538, 1975.
481. NAHORSKI, S. R., K. J. ROGERS, AND B. M. SMITH. Histamine H_2 receptors and cyclic AMP in brain. *Life Sci.* 15: 1887–1894, 1974.
482. NAHORSKI, S. R., K. J. ROGERS, AND B. M. SMITH. Stimulation of adenosine cyclic 3′5′-monophosphate in chick cerebral hemisphere slices: effects of H_1 and H_2 histaminergic agonists and antagonists. *Brain Res.* 126: 287–290, 1977.
483. NAKAHATA, N., M. W. MARTIN, A. R. HUGHES, J. R. HEPLER, AND K. HARDEN. H_1-histamine receptors on human astrocytoma cells. *Mol. Pharmacol.* 29: 188–195, 1986.
484. NAQUET, R., M. DENAVIT, AND D. ALBE-FESSARD. Alterations temporaires ou définitives des zones diencéphaliques corticales chez le chat, leur relation avec l'activité EEG et le sommeil. In: *Aspects anatomofonctionnels de la physiologie du sommeil*, edited by M. Jouvet. Paris: CNRS, 1965, p. 107–131.
485. NAQUET, R., M. DENAVIT, AND D. ALBE-FESSARD. Comparaison entre le rôle du subthalamus et celui de différentes structures bulbomésencéphaliques dans le maintien de la vigilance. *Electroencephalogr. Clin. Neurophysiol.* 20: 149–164, 1966.
486. NATH, C., A. GULATI, K. N. DHAWAN, G. P. GUPTA, AND K. P. BHARGAVA. Evidence for central histaminergic mechanism in foot shock aggression. *Psychopharmacology* 76: 228–231, 1982.
487. NATHANSON, J. A. Cyclic nucleotides and nervous system function. *Physiol. Rev.* 57: 157–256, 1977.
488. NAUTA, W. J. H. Hypothalamic regulation of sleep in rats. An experimental study. *J. Neurophysiol.* 9: 285–316, 1946.
489. NEAME, K. D. Uptake of histidine, histamine and other imidazole derivatives by brain slices. *J. Neurochem.* 11: 655–662, 1964.
490. NEMETH, P. R., C. A. ORT, AND J. D. WOOD. Intracellular study of effects of histamine on electrical behaviour of myenteric neurones in guinea-pig small intestine. *J. Physiol. Lond.* 355: 411–425, 1984.
491. NETTI, C., F. GUIDOBONO, V. R. OLGIATI, V. SIBILIA, AND A. PECILE. Influence of brain histaminergic system on episodic growth hormone secretion in the rat. *Neuroendocrinology* 35: 43–47, 1982.
492. NETTI, C., F. GUIDOBONO, V. R. OLGIATI, V. SIBILIA, AND E. PECILE. Comparison of the effects of histamine H_2-receptor antagonists on prolactin secretion in the rat. *Endocrinology* 113: 412–414, 1983.
493. NETTI, C., F. GUIDOBONO, V. SIBILIA, V. R. OLGIATI, F. PAGINI, AND A. PECILE. Failure of somatostatin antiserum to reverse histamine-induced inhibition of pulsatile growth hormone secretion. *Horm. Res.* 19: 12–17, 1984.
494. NETTI, C., F. GUIDOBONO, V. SIBILIA, V. R. OLGIATI, AND A. PECILE. Histamine agonist and antagonist drugs: interference with CNS control of GH release in rats. *Horm. Res.* 14: 180–191, 1981.
495. NETTI, C., F. GUIDOBONO, V. SIBILIA, I. VILLA, E. CAZZAMALLI, AND A. PECILE. Involvement of brain histamine in basal and stress-induced release of prolactin in the rat. *Agents Actions* 20: 236–238, 1987.
496. NEWSON, B., A. DAHLSTRÖM, L. ENERBACK, AND H. AHLMAN. Suggestive evidence for a direct innervation of mucosal mast cells an electron microscopy study. *Neuroscience* 10: 565–570, 1983.
497. NICHOLSON, A. N. New antihistaminics free of sedative side-effects. *Trends Pharmacol. Sci.* 8: 247–249, 1987.
498. NICHOLSON, A. N., AND B. M. STONE. Antihistamines: impaired performance and the tendency to sleep. *Eur. J. Clin. Pharmacol.* 30: 27–32, 1986.
499. NICOLL, R. A., D. V. MADISON, AND B. LANCASTER. Noradrenergic modulation of neuronal excitability in mammalian hippocampus. In: *Psychopharmacology, the Third Generation of Progress*, edited by H. Y. Meltzer. New York: Raven, 1987, p. 105–112.
500. NIELSEN, S. T. Binding of [^{3}H] ICIA 5165, an H_2-receptor antagonist to guinea-pig gastric mucosa. *Agents Actions* 18: 524–531, 1986.
501. NISHIGAWA, H., H. YAMATODANI, T. NISHIMURA, H. WADA, AND R. CACABELOS. Effect of neurotoxic lesions in the mammillary bodies on the distribution of brain histamine. *Brain Res.* 459: 183–186, 1988.
502. NINKOVIC, M., AND S. P. HUNT. Opiate and histamine H_1 receptors are present on some substance P containing dorsal root ganglion cells. *Neurosci. Lett.* 53: 183–187, 1985.
503. NINKOVIC, M., S. P. HUNT, AND R. W. GLEAVE. Localization of opiate and histamine H_1 receptors in the primate sensory ganglia and spinal cord. *Brain Res.* 241: 197–206, 1982.
504. NISHIBORI, M., R. OISHI, Y. ITOH, AND K. SAEKI. Morphine-induced changes in histamine dynamics in mouse brain. *J. Neurochem.* 46: 719–724, 1985.

506. NISHIBORI, M., R. OISHI, Y. ITOH, AND K. SAEKI. Glucose modulates the release of histamine from the mouse hypothalamus in vitro. *J. Neurochem.* 47: 1761–1767, 1986.
506. NISHIBORI, M., R. OISHI, Y. ITOH, AND K. SAEKI. Effects of Gaba-mimetic drugs on turnover of histamine in the mouse brain. *Jpn. J. Pharmacol.* 41: 403–408, 1986.
507. NISHIBORI, M., R. OISHI, AND K. SAEKI. Histamine turnover in the brain of different mammalian species: implications for neuronal histamine half-life. *J. Neurochem.* 43: 1544–1549, 1984.
508. NISHIZUKA, Y. The role of protein kinase C in cell surface signal transduction and tumor promotion. *Nature Lond.* 308: 693–698, 1984.
509. NISTICO, G., D. ROTROTI, A. DE SARRO, F. NACCARI, AND J. D. STEPHENSON. Central effects of histamine and H_1 and H_2-receptors agonists and antagonists after intraventricular infusion in fowls. *Res. Commun. Chem. Pathol. Pharmacol.* 27: 431–450, 1980.
510. NORRIS, D. B., G. A. GAJTKOWSKI, AND T. J. RISING. Histamine H_2-binding studies in the guinea-pig brain. *Agents Actions* 14: 543–545, 1984.
511. NORTH, R. A., J. T. WILLIAMS, A. M. SURPRENANT, AND M. J. CHRISTIE. μ and δ receptors belong to a family of receptors that are coupled to potassium channels. *Proc Natl. Acad. Sci. USA* 84: 5487–5491, 1987.
512. NOWAK, J. Z. Depolarization-evoked release of dopamine and histamine from brain tissue, and studies on presynaptic dopamine-histamine interaction. *Pol. J. Pharmacol. Pharm.* 37: 369–382, 1985.
513. NOWAK, J. Z. Histaminergic mechanisms in the vertebrate visual system. *J. Pharmacol.* 37: 783–819, 1985.
514. NOWAK, J. Z., J. M. ARRANG, J. C. SCHWARTZ, AND M. GARBARG. Interaction between mianserin, an antidepressant drug, and central H_1- and H_2-histamine-receptors: in vitro and in vivo studies and radioreceptor assay. *Neuropharmacology* 22: 259–266, 1983.
515. NOWAK, J. Z., B. BIELKIEWICZ, AND U. LEBRECHT. Dimaprit induced hypothermia in normal rats: its attenuation by cimetidine and by tricyclic antidepressant drugs. *Neuropharmacology* 18: 783–789, 1979.
516. NOWAK, J. Z., AND J. Z. KULINSKI. The origin and fate of histamine in the rabbit retina. *Neurochem. Int.* 8: 53–58, 1986.
517. OAKES, S. G., P. A. IAIZZO, E. RICHELSON, AND G. POWIS. Histamine-induced intracellular free Ca^{++}, inositol phosphates and electrical changes in murine N1E-115 neuroblastoma cells. *J. Pharmacol. Exp. Ther.* 247: 114–121, 1988.
518. OHSAKO, S., AND T. DEGUCHI. Receptor-mediated regulation of calcium mobilization and cyclic GMP synthesis in neuroblastoma cells. *Biochem. Biophys. Res. Commun.* 122: 333–339, 1984.
519. OISHI, R., Y. ITOH, M. NISHIBORI, AND K. SAEKI. Δ^9-Tetrahydrocannabinol decreases turnover of brain histamine. *J. Pharmacol. Exp. Ther.* 232: 513–518, 1985.
519a. OISHI, R., ITOH, M. NISHIBORI, AND K. SAEKI. Effects of the histamine H_3-agonist (R)-α-methylhistamine and the antagonist thioperamide on histamine metabolism in the mouse and rat brain. *J. Neurochem.* 52: 1388–1392, 1989.
520. OISHI, R., M. NISHIBORI, Y. ITOH, AND K. SAEKI. Diazepam-induced decrease in histamine-turnover in mouse brain. *Eur. J. Pharmacol.* 124: 337–342, 1986.
521. OISHI, R., M. NISHIBORI, AND K. SAEKI. Regional distribution of histamine and *tele*-methylhistamine in the rat, mouse and guinea-pig brain. *Brain Res.* 280: 172–175, 1983.
522. OISHI, R., M. NISHIBORI, AND K. SAEKI. Regional differences in the turnover of neuronal histamine in the rat brain. *Life Sci.* 34: 691–699, 1984.
523. OLIANAS, M., A. P. OLIVER, AND N. H. NEFF. Correlation between histamine-induced neuronal excitability and activation of adenylate cyclase in the guinea pig hippocampus. *Neuropharmacology* 23: 1071–1074, 1984.
524. OLSSON, Y. Mast cells in the nervous system. *Int. Rev. Cytol.* 24: 27–70, 1968.
525. ONODERA, K., AND Y. OGURA. The effect of intraventricular injection of histamine on the behaviour in mice and rats. In: *Advances in Histamine Research*, edited by B. Uvnas and K. Tasaka. Oxford, UK: Permagon, 1981, p. 127–136.
526. ONODERA, K., AND Y. OGURA. Opiate-like actions by intracerebroventricular histamine in mice and its antagonism by naloxone. *Jpn. J. Oral Biol.* 25: 1144–1147, 1983.
527. ONODERA, K., AND Y. OGURA. Effects of histaminergic drugs on muricide induced by thiamine deficiency. *Jpn. J. Pharmacol.* 34: 15–21, 1984.
527a. OOKUMA, K., H. YOSHIMATSU, T. SAKATA, K. FUJIMOTO, AND K. FUKAGAWA. Hypothalamic sites of neuronal histamine on food intake by rats. *Brain Res.* 490: 268–275, 1989.
528. ORR, E. L., AND K. R. PACE. The significance of mast cells as a source of histamine in the mouse brain. *J. Neurochem.* 42: 727–732, 1984.
529. ORR, E. L., AND W. B. QUAY. Hypothalamic 24-hour rhythm in histamine, histidine decarboxylase and histamine-*N*-methyl transferase. *Endocrinology* 96: 941–945, 1975.
530. ORR, E. L., AND W. B. QUAY. Product inhibition of rat brain histamine-*N*-methyltransferase. *J. Neurochem.* 30: 1539–1542, 1978.
531. OSBORNE, N. N., AND S. PATEL. Localisation of histamine immunoreactivity in specific neurones of the gastropod CNS including a cell which has been identified as histaminergic. *Histochemistry* 81: 207–208, 1984.
532. OTTOSSON, A., I. JANSEN, AND L. EDVINSSON. Characterization of histamine receptors in isolated human cerebral arteries. *Br. J. Pharmacol.* 94: 901–907, 1988.
533. OVERTON, D. A. Discriminable effects of antihistamine drugs. *Arch. Int. Psychopharmacodyn. Ther.* 232: 221–226, 1978.
534. OWMAN, C. Neurogenic control of the vascular system: focus on cerebral circulation. In: *Handbook of Physiology. The Nervous System. Intrinsic Regulatory Systems of the Brain.* Bethesda, MD: Am. Physiol. Soc., 1986, sect. 1, vol. IV, chapt. 10, p. 525–580.
535. OWMAN, C., AND J. E. HARDEBO. *Neural Regulation of Brain Circulation: Effects of Neurotransmitters and Neuromodulators.* Amsterdam: Elsevier, 1986.
536. OZAWA, K., Y. NOMURA, AND T. SEGAWA. Histamine acting on H_2 receptors stimulates phospholipid methylation in synaptic membranes of rat brain. *J. Neurochem.* 48: 1392–1398, 1987.
537. OZAWA, K., AND T. SEGAWA. Histamine increases phospholipid methylation and H_2-receptor-adenylate cyclase coupling in rat brain. *J. Neurochem.* 50: 1551–1558, 1988.
538. PAAKKARI, I., H. KARPPANEN, AND P. PAAKKARI. Histaminergic and related mechanisms in the central control of blood pressure. *Acta Med. Scand. Suppl.* 625: 81–85, 1979.
539. PALACIOS, J. M., M. GARBARG, G. BARBIN, AND J. C. SCHWARTZ. Pharmacological characterization of histamine receptors mediating the stimulation of cyclic AMP accumulation in slices from guinea pig hippocampus. *Mol. Pharmacol.* 14: 971–982, 1978.
540. PALACIOS, J. M., G. MENGOD, M. GRAU, F. PICATOSTE, AND I. BLANCO. Pyridoxal-5'-phosphate as a cofactor for rat brain histidine decarboxylase. *J. Neurochem.* 30: 213–216, 1978.
541. PALACIOS, J. M., G. MENGOD, F. PICATOSTE, M. GRAU, AND I. BLANCO. Properties of rat brain histidine decarboxylase. *J. Neurochem.* 27: 1455–1460, 1976.
542. PALACIOS, J. M., J. C. SCHWARTZ, AND M. GARBARG. High affinity binding of ^{3}H-histamine in rat brain. *Eur. J. Pharmacol.* 52: 443–444, 1978.
543. PALACIOS, J. M., J. K. WAMSLEY, AND M. J. KUHAR. The distribution of histamine H_1-receptors in the rat brain: an autoradiographic study. *Neuroscience* 6: 15–37, 1981.
544. PALACIOS, J. M., J. K. WAMSLEY, AND M. J. KUHAR. GABA benzodiazepine and histamine-H_1 receptors in the guinea pig cerebellum: effects of kainic acid injections studied by autoradiographic methods. *Brain Res.* 214: 155–162, 1981.
545. PALACIOS, J. M., W. S. YOUNG III, AND M. J. KUHAR. Autoradiographic localization of H_1-histamine receptors in brain using ^{3}H-mepyramine: preliminary studies. *Eur. J. Pharmacol.* 58: 295–304, 1979.
546. PALMER, G. C. Regional distribution of neurohumoral responsive adenylate cyclase in rabbit brain microvessels. *Neurosci. Lett.* 21: 207–210, 1981.
547. PALMER, G. C., R. B. CHRONISTER, AND S. J. PALMER. Adenylate cyclase responses to neurohumoral agonists in microvascular elements of the rat brain. *J. Neurobiol.* 11: 503–508, 1980.

548. PALMER, G. C., AND S. J. PALMER. 5'-Guanylyl-imidodiphosphate action on adenylate cyclase in homogenates of rat cerebral cortex plus neuronal and capillary fractions. *Life Sci.* 23: 207–216, 1978.

549. PANULA, P., M. AIRAKSINEN, U. PIRVOLA, AND E. KOTILAINEN. Histamine-immunoreactive neurons and nerve fibers in human brain (Abstract). *Soc. Neurosci. 18th Toronto Canada 1988*, p. 211.

549a. PANULA, P., M. S. AIRAKSINEN, U. PIRVOLA, AND E. KOTILAINEN. A histamine-containing neuronal system in human brain. *Neuroscience* 34: 127–132, 1990.

550. PANULA, P., O. HAPPOLA, M. S. AIRAKSINEN, S. AUVINEN, AND A. VIRKAMÄKI. Carbodiimide as a tissue fixative in histamine immunohistochemistry and its application in developmental neurobiology. *J. Histochem. Cytochem.* 36: 259–269, 1988.

551. PANULA, P., U. PIRVOLA, S. AUVINEN, AND M. S. AIRAKSINEN. Histamine-immunoreactive nerve fibers in the rat brain. *Neuroscience* 28: 585–610, 1989.

552. PANULA, P., H. Y. T. YANG, AND E. COSTA. Histamine-containing neurons in the rat hypothalamus. *Proc. Natl. Acad. Sci. USA* 81: 2572–2576, 1984.

553. PATEL, B. T., N. TUDBALL, H. WADA, AND T. WATANABE. Adenosine deaminase and histidine decarboxylase coexist in certain neurons of the rat brain. *Neurosci. Lett.* 63: 185–189, 1986.

553a. PAXINOS, G., AND C. WATSON. *The Rat Brain in Stereotaxic Coordinates.* Sydney, Australia: Academic, 1982.

554. PEARCE, A. G. E. The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the APUD series and the embryologic, physiologic, and pathologic implications of the concept. *J. Histochem. Cytochem.* 17: 303–313, 1969.

555. PEARCE, L. A., AND S. M. SCHANBERG. Histamine and spermidine content in rat brain during development. *Science Wash. DC* 166: 1301–1302, 1969.

556. PELLMAR, T. C. Histamine decreases calcium-mediated potassium current in guinea pig hippocampal CA1 pyramidal cells. *J. Neurophysiol.* 55: 727–738, 1986.

557. PEROUTKA, S. J., M. A. MOSKOWITZ, J. F. REINHARD, AND S. H. SNYDER. Neurotransmitter receptor binding in bovine cerebral-microvessels. *Science Wash. DC* 208: 610–612, 1980.

558. PEROUTKA, S. J., AND S. H. SNYDER. Mianserin: differential labeling of serotonin and histamine, receptors in rat brain. *J. Pharmacol. Exp. Ther.* 216: 142–148, 1981.

559. PERSINGER, M. A. Mast cells in the brain: possibilities for physiological psychology. *Physiol. Psychol.* 5: 166–176, 1977.

560. PHILIPPU, A. Possible involvement of brain histamine in the regulation of blood pressure. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 335–340.

561. PHILIPPU, A., R. HAGEN, U. HANESCH, AND U. WALDMANN. Changes in the arterial blood pressure increase the release of endogenous histamine in the hypothalamus of anaesthetized cats. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 323: 162–167, 1983.

562. PHILIPPU, A., U. HANESCH, R. HAGEN, AND R. L. ROBINSON. Release of endogenous histamine in the hypothalamus of anaesthetized cats and conscious, freely moving rabbits. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 321: 282–286, 1982.

563. PHILLIS, J. W., G. K. KOSTOPOULOS, AND A. ODUTOLA. On the specificity of histamine H_2-receptor antagonists in the rat cerebral cortex. *Can. J. Physiol. Pharmacol.* 53: 1205–1209, 1975.

564. PHILLIS, J. W., A. K. TEBECIS, AND D. H. YORK. Histamine and some antihistamines: action on cerebral cortical neurones. *Br. J. Pharmacol. Chemother.* 33: 426–440, 1968.

565. PICATOSTE, F., I. BLANCO, AND J. M. PALACIOS. The presence of two cellular pools of rat brain histamine. *J. Neurochem.* 29: 735–738, 1977.

566. PILC, A., AND J. Z. NOWAK. The influence of 4-methylhistamine, an agonist of histamine H_2 receptors on body temperature in rats. *Neuropharmacology* 19: 773–776, 1980.

567. POLLARD, H., S. BISCHOFF, C. LLORENS-CORTES, AND J. C. SCHWARTZ. Histidine decarboxylase and histamine in discrete nuclei of rat hypothalamus and the evidence for mast-cells in the median eminence. *Brain Res.* 118: 509–513, 1976.

568. POLLARD, H., S. BISCHOFF, AND J. C. SCHWARTZ. Decreased histamine synthesis in the rat brain by hypnotics and anaesthetics. *J. Pharm. Pharmacol.* 25: 920–922, 1973.

569. POLLARD, H., S. BISCHOFF, AND J. C. SCHWARTZ. Increased synthesis and release of ^{3}H-histamine in rat brain by reserpine. *Eur. J. Pharmacol.* 24: 399–401, 1973.

570. POLLARD, H., S. BISCHOFF, AND J. C. SCHWARTZ. Modifications of brain histamine metabolism induced by antihistamines. *Agents Actions* 3: 190–194, 1973.

571. POLLARD, H., S. BISCHOFF, AND J. C. SCHWARTZ. Turnover of histamine in rat brain and its decrease under barbiturate anaesthesia. *J. Pharmacol. Exp. Ther.* 190: 88–99, 1974.

572. POLLARD, H., C. LLORENS-CORTES, G. BARBIN, M. GARBARG, AND J. C SCHWARTZ. Histamine and histidine decarboxylase in brain stem nuclei: distribution and decrease after lesions. *Brain Res.* 157: 178–181, 1978.

573. POLLARD, H., I. PACHOT, P. LEGRAIN, G. BUTTIN, AND J. C. SCHWARTZ. Development of a monoclonal antibody against L-histidine decarboxylase as a selective tool for the localisation of histamine synthetising cells. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 103–118.

574. POLLARD, H., I. PACHOT, AND J. C. SCHWARTZ. Monoclonal antibody against L-histidine decarboxylase for localization of histaminergic cells. *Neurosci. Lett.* 54: 53–58, 1985.

575. POLLARD, H., I. PACHOT, J. C. SCHWARTZ, M. LANGE, P. LEGRAIN, AND G. BUTTIN. Production d'anticorps monoclonaux anti-L-histidine décarboxylase. *C. R. Seances Acad. Sci. Ser. III Sci. Vie* 297: 553–556, 1983.

576. POLLARD, H., AND J. C. SCHWARTZ. L-Histidine decarboxylase, a marker of histaminergic neurons. In: *Neuromethods. Neurotransmitter Enzymes*, edited by A. A. Bouton, G. B. Baker, and P. H. Yu. Clifton, NJ: Humana, 1986, vol. 5, p. 205–223.

577. POLLARD, H., AND J. C. SCHWARTZ. Histamine neuronal pathways and their functions. *Trends Neurosci.* 10: 86–89, 1987.

578. PONTIROLI, A. E., AND G. POZZA. Histamine stimulates prolactin release in normal man. *Acta Endocrinol.* 88: 23–28, 1978.

579. POPIELSKI, B. Influence de l'histamine sur la sécrétion du sac gastrique chez la grenouille. *C. R. Seances Soc. Biol. Paris* 100: 275–296, 1929.

580. PORTALEONE, P., G. PAGNINI, A. CRISPINO, AND E. GENAZZANI. Histamine-sensitive adenylate cyclase in hypothalamus of rat brain: H_1- and H_2-receptors. *J. Neurochem.* 51: 1371–1374, 1978.

581. POULAKOS, J. J., AND S. B. GERTNER. Studies on the desensitization of the central cardiovascular responses of histamine. *J. Pharmacol. Exp. Ther.* 238: 730–736, 1986.

582. PRAST, H., V. GUIRATI, S. WALSER, AND A. PHILIPPU. Histamine, histidine decarboxylase and histamine-*N*-methyltransferase in brain areas of spontaneously hypertensive rats. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 338: 573–576, 1988.

583. PRAST, H., A. SAXER, AND A. PHILIPPU. Pattern of in vivo release of endogenous histamine in the mamillary body and the amygdala. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 337: 63–67, 1988.

584. PRELL, G. D., AND J. P. GREEN. Histamine as a neuroregulator. *Annu. Rev. Neurosci.* 9: 209–254, 1986.

585. PRELL, G. D., J. K. KHANDELWAL, R. S. BURNS, AND J. P. GREEN. Histamine metabolites in cerebrospinal fluid of the rhesus monkey (*Macaca mulatta*): cisternal-lumbar concentration gradients. *J. Neurochem.* 50: 1194–1199, 1988.

586. PSYCHOYOS, S. H_1- and H_2-histamine receptors linked to adenylate cyclase in cell-free preparations of guinea-pig cerebral cortex. *Life Sci.* 28: 2155–2162, 1976.

587. PSYCHOYOS, S., J. DOVE, B. STROWBRIDGE, AND I. NUSYNOWITZ. Highly activatable adenylate cyclase in 2-[^{3}H]adenine-prelabeled vesicles prepared from guinea pig cerebral cortex by a simplified procedure. *J. Neurochem.* 38: 1437–1445, 1982.

588. PUIL, E., I. SPIGELMAN, A. EISEN, AND S.-U. KIM. Electrophysiological responses of human spinal neurons in culture. *Neurosci. Lett.* 71: 77–82, 1986.

589. QUACH, T. T., A. M. DUCHEMIN, C. ROSE, AND J. C. SCHWARTZ. In vivo occupation of cerebral histamine H_1-receptors evaluated with ^{3}H-mepyramine may predict sedative properties of psychotropic drugs. *Eur. J. Pharmacol.* 60: 391–392, 1979.

590. QUACH, T. T., A. M. DUCHEMIN, C. ROSE, AND J. C. SCHWARTZ. ^{3}H-glycogen hydrolysis elicited by histamine in mouse brain slices: selective involvement of H_1 receptors. *Mol. Pharmacol.* 17: 301–308, 1980.
591. QUACH, T. T., A. M. DUCHEMIN, C. ROSE, AND J. C. SCHWARTZ. Labeling of histamine H_1-receptors in the brain of the living mouse. *Neurosci. Lett.* 17: 49–54, 1980.
592. QUACH, T. T., A. M. DUCHEMIN, C. ROSE, AND J. C. SCHWARTZ. Specific desensitization of histamine H_1 receptor-mediated [^{3}H]glycogen hydrolysis in brain slices. *Mol. Pharmacol.* 20: 331–338, 1981.
593. QUACH, T. T., A. M. DUCHEMIN, C. ROSE, AND J. C. SCHWARTZ. [^{3}H]glycogenolysis in brain slices mediated by β-adrenoceptors: comparison of physiological response and [^{3}H]dihydroalprenolol binding parameters. *Neuropharmacology* 27: 629–635, 1988.
594. QUACH, T. T., C. ROSE, A. M. DUCHEMIN, AND J. C. SCHWARTZ. Glycogenolysis induced by serotonin in brain: identification of a new class of receptors. *Nature Lond.* 298: 373–375, 1982.
595. QUACH, T. T., C. ROSE, AND J. C. SCHWARTZ. [^{3}H]glycogen hydrolysis in brain slices: responses to neurotransmitters and modulation of noradrenaline receptors. *J. Neurochem.* 30: 1336–1343, 1978.
596. RABIN, B. M., W. A. HUNT, AND J. LEE. Studies on the role of central histamine in the acquisition of a radiation-induced conditioned taste aversion. *Radiat. Res.* 90: 609–620, 1982.
597. RANSON, S. W. Somnolence caused by hypothalamic lesion in the monkey. *Arch. Neurol. Psychiatry* 41: 1–23, 1939.
598. RAY, A., K. K. SHARMA, AND P. SEN. Effect of histaminergic drugs on footshock-induced aggressive behaviour in rats. *Eur. J. Pharmacol.* 73: 217–219, 1981.
599. REICHELT, K. L., P. D. EDMINSON, AND E. KVAMME. The formation of peptido-amines from constituent amino-acids and histamine in hypothalamic tissue. *J. Neurochem.* 26: 811–815, 1976.
600. REILLY, M. A. Biogenic amine participation in histamine stimulation of ACTH release. *Agents Actions* 14: 630–632, 1976.
601. REILLY, M. A., AND R. W. SCHAYER. Histamine formation and catabolism in mouse brain (Abstract). *Federation Proc.* 29: 2083, 1970.
602. REILLY, M. A., AND R. W. SCHAYER. In vivo studies on histamine catabolism and its inhibition. *Br. J. Pharmacol.* 38: 478–489, 1970.
603. REILLY, M. A., AND R. W. SCHAYER. Further studies on histamine catabolism in vivo. *Br. J. Pharmacol.* 43: 349–358, 1971.
604. REINER, P. B., AND E. G. MCGEER. Electrophysiological properties of cortically projecting histamine neurons of the rat hypothalamus. *Neurosci. Lett.* 73: 43–47, 1987.
605. REINER, P. B., K. SEMBA, H. C. FIBIGER, AND E. G. MCGEER. Ontogeny of histidine decarboxylase immunoreactive neurons in the tuberomammillary nucleus of the rat hypothalamus: time of origin and development of transmitter phenotype. *J. Comp. Neurol.* 276: 304–311, 1988.
606. REINER, P. B., K. SEMBA, T. WATANABE, AND H. WADA. En Bloc immunohistochemistry reveals extensive distribution of histidine decarboxylase-immunoreactive neurons on the ventral surface of the rat hypothalamus. *Neurosci. Lett.* 77: 137–142, 1987.
607. REITE, O. B. Comparative physiology of histamine. *Physiol. Rev.* 52: 778–819, 1972.
608. RENAUD, L. P. Histamine microiontophoresis on identified hypothalamic neurons: 8 patterns of response in the ventro-medial nucleus of the rat. *Brain Res.* 115: 339–344, 1976.
609. RICHELSON, E. Histamine H_1 receptor-mediated guanosine 3′,5′-monophosphate formation by cultured mouse neuroblastoma cells. *Science Wash. DC* 201: 69–71, 1978.
610. RICHELSON, E. Tricyclic antidepressants block histamine H_1 receptors of mouse neuroblastoma cells. *Nature Lond.* 274: 176–177, 1978.
611. RICHELSON, E. Histamine receptors, cyclic nucleotides and psychotic drugs. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 237–247.
612. RISING, T. J., AND D. B. NORRIS. Histamine H_2-receptor radioligand binding studies. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 61–68.
613. RISING, T. J., D. B. NORRIS, S. E. WARRANDER, AND T. P. WOOD. High affinity ^{3}H-cimetidine binding in guinea-pig tissues. *Life Sci.* 27: 199–206, 1980.
614. RIVIER, C., AND W. VALE. Effects of γ-aminobutyric acid and histamine on prolactin secretion in the rat. *Endocrinology* 101: 506–511, 1977.
615. ROBERTS, F., AND C. R. CALCUTT. Histamine and the hypothalamus. *Neuroscience* 9: 721–739, 1983.
616. ROBINSON-WHITE, A., AND M. A. BEAVEN. Presence of histamine and histamine-metabolizing enzyme in rat and guinea-pig microvascular endothelial cells. *J. Pharmacol. Exp. Ther.* 223: 440–445, 1982.
617. RODBELL, M. The role of hormone receptors and GTP-regulatory proteins in membrane transduction. *Nature Lond.* 284: 17–22, 1980.
618. ROGERS, M., K. R. DISMUKES, AND J. W. DALY. Histamine-elicited accumulations of cyclic adenosine 3′,5′-monophosphate in guinea-pig brain slices: effect of H_1- and H_2-antagonists. *J. Neurochem.* 25: 531–534, 1975.
619. RONNBERG, A. L., AND J. C. SCHWARTZ. Répartition régionale de l'histamine dans le cerveau de rat *C. R. Hebd. Seances Acad. Sci. Ser. D Sci. Nat.* 268: 2376–2379, 1969.
620. ROSE, C., T. T. QUACH, C. LLORENS-CORTES, AND J. C. SCHWARTZ. Relationship between occupation of cerebral H_1 receptors and sedative properties of antihistamines. *Arzneim. Forsch.* 32: 1171–1173, 1982.
621. ROTTER, A., AND A. FROSTHOLM. Cerebellar histamine H_1 receptor distribution: an autoradiographic study of purkinje cell degeneration, staggerer, weaver, and reeler mutant mouse strains. *Brain Res. Bull.* 16: 205–214, 1986.
622. RUAT, M., M. L. BOUTHENET, J. C. SCHWARTZ, AND C. R. GANELLIN. Unique histamine H_2-receptor isoform in heart. *J. Neurochem.* 55: 379–385, 1990.
623. RUAT, M., M. KÖRNER, M. GARBARG, C. GROS, J. C. SCHWARTZ, W. TERTUE, AND C. R. GANELLIN. Characterization of histamine H_1-receptor binding peptides in guinea-pig brain using [^{125}I]iodoazidiophenpyramine, an irreversible specific photoaffinity probe. *Proc. Natl. Acad. Sci. USA* 85: 2743–2747, 1988.
624. RUAT, M., AND J. C. SCHWARTZ. Photoaffinity labeling and electrophoretic identification of the H_1-receptor: comparison of several brain regions and animal species. *J. Neurochem.* 53: 335–339, 1989.
624a. RUAT, M., E. TRAIFFORT, M. L. BOUTHENET, J. C. SCHWARTZ, J. HIRSCHFELD, A. BUSCHAUER, AND W. SCHUNACK. Reversible and irreversible labeling and autoradiographic localization of the cerebral histamine H_2-receptor using [^{125}I]iodinated probes. *Proc. Natl. Acad. Sci. USA* 87: 1658–1662, 1990.
625. RUDOLPH, C., G. E. RICHARDS, S. KAPLAN, AND W. F. GANONG. Effect of intraventricular histamine on hormone secretion in dogs. *Neuroendocrinology* 23: 169–177, 1979.
626. RUMORE, M. M., D. PHARM, AND D. A. SCHLICHTING. Analgesic effects of antihistaminics. *Life Sci.* 36: 403–416, 1985.
627. RUMORE, M. M., AND D. A. SCHLICHTING. Clinical efficacy of antihistaminics as analgesics. *Pain* 25: 7–22, 1986.
628. SAAVEDRA, J. M., M. J. BROWSTEIN, AND M. PALKOVITS. Distribution of catechol-O-methyltransferase, histamine *N*-methyltransferase and monoamine oxidase in specific areas of the rat brain. *Brain Res.* 118: 152–156, 1976.
629. SAEKI, K., R. OISHI, AND M. NISHIBORI. Simultaneous determination of histamine and *tele*-methylhistamine in the mammalian central nervous system and histamine turnover measurements. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 173–184.
630. SAFFRAN, M., AND A. V. SCHALLY. The release of corticotrophin by anterior pituitary tissue in vitro. *Can. J. Biochem. Physiol.* 33: 408–415, 1955.
631. SAKAI, K., B. H. MARKS, J. M. GEORGE, AND A. KOESTNER. The isolated organ-cultured supraoptic nucleus as a neurophar-

macological test system. *J. Pharmacol. Exp. Ther.* 190: 482–491, 1974.

682. SAKAI, K., D. SALVERT, K. KITAHAMA, H. KIMURA, T. MAEDA, AND M. JOUVET. Projections ascendantes et descendantes des neurones de l'hypothalamus postérieur immunoréactifs à la sérotonine après administration de 5-hydroxytryptophane chez le chat. *C. R. Seances Acad. Sci. Ser. III Sci. Vie* 296: 1013–1018, 1983.
683. SAKAMOTO, Y., K. WATANABE, H. HAYASHI, Y. TAGUCHI, AND H. WADA. Effect of various compounds on histidine decarboxylase activity: active site mapping. *Agents Actions* 17: 32–37, 1985.
684. SAKATA, T., K. FUKAGAWA, K. FUJIMOTO, H. YOSHIMATSU, T. SHIRAISHI, AND H. WADA. Feeding induced by blockade of histamine H_1-receptor in rat brain. *Experientia Basel* 44: 216–218, 1988.
685. SAKATA, T., K. OOKUMA, K. FUKAGAWA, K. FUJIMOTO, H. YOSHIMATSU, T. SHIRAISHI, AND H. WADA. Blockade of the histamine H_1-receptor in the rat ventromedial hypothalamus and feeding elicitation. *Brain Res.* 441: 403–407, 1988.
686. SAKUMOTO, T., K. SAKAI, M. JOUVET, H. KIMURA, AND T. MAEDA. Neurones de type APUD dans le système nerveux central: mise en évidence d'un groupe de neurones dans l'hypothalamus ventrolatéral du rat et du chat révélé par l'immunohistochimie de la sérotonine après administration de 5-hydroxytryptophane. *C. R. Hebd. Seances Acad. Sci* 295: 631–635, 1982.
687. SAKUMOTO, T., K. SAKAI, M. JOUVET, H. KIMURA, AND T. MAEDA. 5-HT immunoreactive hypothalamic neurons in rat and cat after 5-HTP administration. *Brain Res. Bull.* 12: 721–733, 1984.
688. SALLANON, M., K. SAKAI, C. BUDA, M. PUYMARTIN, AND M. JOUVET. Augmentation du sommeil paradoxal, induite par l'injection d'acide biotènique dans l'hypothalamus ventrolateral postérieur chez le chat. *C. R. Hebd. Seances Acad. Sci.* 303: 175–179, 1986.
689. SASTRY, B. S. R., AND J. W. PHILLIS. Depression of rat cerebral cortical neurones by H_1 and H_2 histamine receptor agonists. *Eur. J. Pharmacol.* 38: 269–273, 1976.
690. SASTRY, B. S. R., AND J. W. PHILLIS. Evidence for an ascending inhibitory histaminergic pathway to the cerebral cortex. *Can. J. Physiol. Pharmacol.* 54: 762–786, 1976.
641. SATAYAVIDAD, J., AND E. B. KIRSTEIN. Iontophoretic studies of histamine and histamine antagonists in the feline vestibular nuclei. *Eur. J. Pharmacol.* 41: 17–26, 1977.
642. SAVANY, A., AND L. CRONENBERGER. Purification and détection de plusieurs formes moléculaires de l'histidine decarboxylase de la muqueuse gastrique de rat. *Biochim. Biophys. Acta* 526: 247–255, 1978.
643. SAVANY, A., AND L. CRONENBERGER. Isolation and properties of multiple forms of histidine decarboxylase from rat gastric mucosa. *Biochem. J.* 205: 405–412, 1982.
644. SAWYER, C. H. Rhinencephalic involvement in pituitary activation by intraventricular histamine in the rabbit under nembutal anesthesia. *Am. J. Physiol.* 180: 37–46, 1955.
645. SCHAYER, R. W. Catabolism of physiological quantities of histamine in vivo. *Physiol. Rev.* 39: 116–120, 1959.
646. SCHAYER, R. W. Relationship of induced histidine decarboxylase activity and histamine synthesis to shock from stress and from endotoxin. *Am. J. Physiol.* 198: 1187–1192, 1960.
647. SCHAYER, R. W. Biogenesis of histamine. In: *Handbook of Experimental Pharmacology, Chemistry, Metabolism and Physiological and Pharmacological Actions*, edited by M. Rocha e Silva. Berlin: Springer-Verlag, 1978, vol. 18, pt. 2, p. 109–122.
648. SCHAYER, R. W., AND M. A. REILLY. In vivo formation and catabolism of ^{14}C-histamine in mouse brain. *J. Neurochem.* 17: 1649–1655, 1970.
649. SCHAYER, R. W., AND M. A. REILLY. Formation and fate of histamine in rat and mouse brain. *J. Pharmacol. Exp. Ther.* 184: 33–40, 1973.
650. SCHAYER, R. W., AND M. A. REILLY. Effect of histidine decarboxylase inhibitors and other drugs on histamine formation in vivo. *Agents Actions* 4: 132–138, 1974.
651. SCHAYER, R. W., AND M. A. REILLY. Histamine formaton in guinea-pig brain and other tissues; effect of alpha-methyl-dopa. *Agents Actions* 4: 139–142, 1974.
652. SCHLICKER, E., R. BETZ, AND M. GOTHERT. Histamine H_3 receptor-mediated inhibition of serotonin release in the rat brain cortex. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 337: 588–590, 1988.
652a. SCHLICKER, E., K. FINK, M. HINTERTHANER, AND M. GOTHERT. Inhibition of noradrenaline release in the rat brain cortex via presynaptic H_3-receptors. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 340: 633–638, 1989.
653. SCHULTZ, J., AND J. DALY. Accumulation of adenosine cyclic 3':5'-monophosphate in cerebral cortical slices from rat and mouse: stimulatory effect of α- and β-adrenergic agents and adenosine. *J. Neurochem.* 21: 1319–1326, 1973.
654. SCHWARTZ, J. C. Histamine as a transmitter in brain. *Life Sci.* 17: 503–518, 1975.
655. SCHWARTZ, J. C. Histaminergic mechanisms in brain. *Annu. Rev. Pharmacol. Toxicol.* 17: 325–339, 1977.
656. SCHWARTZ, J. C. Histamine receptors in brain. *Life Sci.* 25: 895–912, 1979.
657. SCHWARTZ, J. C., Y. AGID, M. L. BOUTHENET, F. JAVOY-AGID, C. LLORENS-CORTES, M. P. MARTRES, H. POLLARD, N. SALES, AND H. TAQUET. Neurochemical investigations into the human area postrema. In: *Nausea and Vomiting: Mechanisms and Treatment*, edited by C. J. Davis, G. V. Lake-Bakaar, and D. G. Grahame-Smith. Berlin: Springer-Verlag, 1986, p. 19–30.
658. SCHWARTZ, J. C., J. M. ARRANG, AND M. GARBARG. Three classes of histamine receptors in brain. *Trends. Pharmacol. Sci.* 7: 24–28, 1986.
659. SCHWARTZ, J. C., J. M. ARRANG, M. GARBARG, AND W. SCHUNACK. Three classes of histamine receptors in brain: targets for novel drugs? In: *Innovative Approaches in Drug Research*, edited by A. F. Harms. Amsterdam: Elsevier, 1986, p. 73–89.
660. SCHWARTZ, J. C., G. BARBIN, M. BAUDRY, M. GARBARG, M. P. MARTRES, H. POLLARD, AND M. VERDIERE. Metabolism and functions of histamine in the brain. In: *Current Developments in Psychopharmacology*, edited by W. B. Essman and L. Valzelli. New York: Spectrum, 1979, vol. 5, p. 173–261.
661. SCHWARTZ, J. C., G. BARBIN, A. M. DUCHEMIN, M. GARBARG, C. LLORENS, H. POLLARD, T. T. QUACH, AND C. ROSE. Histamine receptors in the brain and their possible functions. In: *Pharmacology of Histamine Receptors*, edited by C. R. Ganellin and M. E. Parsons. Bristol, UK: Wright, 1982, p. 351–391.
662. SCHWARTZ, J. C., G. BARBIN, A. M. DUCHEMIN, M. GARBARG, H. POLLARD, T. T. QUACH, AND C. ROSE. Functional role of histamine in the brain. In: *Neuropharmacology of Central Nervous System and Behavioral Disorders*, edited by G. C. Palmer. New York: Academic, 1981, p. 539–570.
663. SCHWARTZ, J. C., G. BARBIN, M. GARBARG, C. LLORENS-CORTES, J. M. PALACIOS, AND H. POLLARD. Histaminergic systems in brain. In: *Advances in Pharmacology and Therapeutics. Neurotransmitters*, edited by P. Simon. Oxford, UK: Pergamon, 1978, vol. 2, p. 171–180.
664. SCHWARTZ, J. C., M. BAUDRY, F. CHAST, H. POLLARD, S. BISCHOFF, AND M. S. KRISHNAMOORTHY. Histamine in the brain: importance of transmethylation processes and their regulation. In: *Metabolic Regulation and Functional Activity in the Central Nervous System*, edited by E. Genazzani and H. Herken. Berlin: Springer-Verlag, 1978, p. 172–184.
665. SCHWARTZ, J. C., M. GARBARG, U. LEBRECHT, J. NOWAK, H. POLLARD, E. RODERGAS, C. ROSE, T. T. QUACH, J. L. MORGAT, AND J. ROY. Histaminergic systems in brain: studies on localisation and actions. In: *Advances in Histamine Research*, edited by B. Uvnas and K. Tasaka. Oxford, UK: Pergamon, 1982, p. 71–80.
666. SCHWARTZ, J. C., M. GARBARG, AND H. POLLARD. Histaminergic transmission in the brain. In: *Handbook of Physiology. The Nervous System. Intrinsic Regulatory Systems of the Brain.* Bethesda, MD: Am. Physiol. Soc., 1986, sect. 1, vol. IV, chapt. 5, p. 257–316.
667. SCHWARTZ, J. C., C. LAMPART, AND C. ROSE. Properties and

regional distribution of histidine decarboxylase in rat brain. *J. Neurochem.* 17: 1527–1534, 1970.
668. SCHWARTZ, J. C., C. LAMPART, AND C. ROSE. Histamine formation in rat brain in vivo: effects of histidine loade. *J. Neurochem.* 19: 801–810, 1972.
669. SCHWARTZ, J. C., C. LAMPART, C. ROSE, M. C. REHAULT, S. BISCHOFF, AND H. POLLARD. Histamine formation in rat brain during development. *J. Neurochem.* 18: 1787–1789, 1971.
670. SCHWARTZ, J. C., J. M. PALACIOS, G. BARBIN, T. T. QUACH, M. GARBARG, H. L. HAAS, AND P. WOLF. Histamine receptors in mammalian brain: characteristics and modifications studied electrophysiologically and biochemically. In: *Histamine Receptors*, edited by T. Yellin. New York: Spectrum, 1979, p. 161–183.
671. SCHWARTZ, J. C., H. POLLARD, S. BISCHOFF, M. C. REHAULT, AND M. VERDIERE. Catabolism of ^{3}H-histamine in the rat brain after intracisternal administration. *Eur. J. Pharmacol.* 16: 326–335, 1971.
672. SCHWARTZ, J. C., H. POLLARD, AND T. T. QUACH. Histamine as a neurotransmitter in mammalian brain: neurochemical evidence. *J. Neurochem.* 35: 26–33, 1980.
673. SCHWARTZ, J. C., A. L. RÖNNBERG, Y. COHEN, AND G. VALETTE. Histamine formation in rat stomach: study of regulation mechanism. *Eur. J. Pharmacol.* 5: 272–276, 1969.
674. SCHWARTZ, J. C., C. ROSE, AND H. CAILLENS. Metabolism of methylhistamine formed through a new pathway: decarboxylation of L-3-methylhistidine. *J. Pharmacol. Exp. Ther.* 184: 766–779, 1973.
675. SEGAL, M. Histamine produces a Ca^{2+}-sensitive depolarization of hippocampal pyramidal cells in vitro. *Neurosci. Lett.* 19: 67–72, 1980.
676. SEGAL, M. Histamine modulates reactivity of hippocampal CA3 neurons to afferent stimulation in vitro. *Brain Res.* 213: 443–448, 1981.
677. SELTZER, A. M., AND A. O. DONOSO. Involvement of specific receptors in the histamine stimulation of the pituitary-corticoadrenal system in the rat. *Neuroendocrinol. Lett.* 4: 299–304, 1982.
678. SELTZER, A. M., A. O. DONOSO, AND E. PODESTA. Restraint stress stimulation of prolactin and ACTH secretion: role of brain histamine. *Physiol. Behav.* 36: 251–255, 1986.
679. SENBA, E. P. E. DADDONA, T. WATANABE, J. Y. WU, AND J. I. NAGY. Coexistence of adenosine deaminase, histidine-decarboxylase and glutamate decarboxylase in hypothalamic neurons of the rat. *J. Neurosci.* 5: 3393–3402, 1985.
680. SERCOMBE, R., C. VERRECCHIA, V. PHILIPSON, N. OUDART, V. DIMITRIADOU, C. BOUCHAUD, AND J. SEYLAZ. Histamine-induced constriction and dilatation of rabbit middle cerebral arteries in vitro: role of the endothelium. *Blood Vessels* 23: 137–153, 1986.
681. SEYBOLD, V. S., AND B. J. WILCOX. Distribution of neurotransmitter binding sites in the cat median eminence. *Neuroendocrinology* 46: 32–38, 1987.
682. SHARPE, D. C., M. A. MELVIN, J. G. MILLS, W. L. BURLAND, AND G. V. GROOM. The effect of histamine H_2-receptor antagonists on plasma prolactin. In: *Further Experience With H_2-Receptor Antagonists in Peptic Ulcer Disease and Progress in Histamine Research*, edited by A. Torsoli, P. E. Lucchelli, and R. W. Brimblecombe. Amsterdam: Excerpta Med., 1980, p. 366–370.
683. SHARPE, D. C., M. A. MELVIN, J. G. MILLS, W. L. BURLAND, AND G. V. GROOM. Prolactin responses to histamine H_2-receptor antagonists. *Acta Endocrinol.* 95: 303–313, 1980.
684. SHAW, G. G. Hypothermia produced in mice by histamine acting on the central nervous system. *Br. J. Pharmacol.* 42: 205–214, 1971.
685. SHEINER, J. B., P. MORRIS, AND G. H. ANDERSON. Food intake suppression by histidine. *Pharmacol. Biochem. Behav.* 23: 721–726, 1985.
686. SHIMIZU, H., C. CREVELING, AND J. DALY. Stimulated formation of adenosine cyclic 3′:5′-phosphate in cerebral cortex: synergism between electrical activity and biogenic amines. *Proc. Natl. Acad. Sci. USA* 65: 1033–1040, 1970.
687. SHIMIZU, H., S. TANAKA, T. SUZUKI, AND Y. MATSUKADO. The response of human cerebrum adenyl cyclase to biogenic amines. *J. Neurochem.* 18: 1157–1161, 1971.
688. SHIROUZU, M., H. KIMURA, T. YAMAMOTO, J. OCHI, AND K. INAGAWA. Production of new type of antisera to thyrotropin releasing hormone (TRH) using carbodiimide coupling and application to immunohistochemistry. *Kurume Med. J.* 30: 1–9, 1985.
689. SHONK, R. F., AND T. W. RALL. Ontogeny of adenosine 3′,5′-monophosphate metabolism in guinea-pig cerebral cortex. I. Development of responses to histamine, norepinephrine and adenosine. *Mol. Cell. Biochem.* 73: 141–155, 1977.
690. SIGGINS, G. R., B. J. HOFFER, AND F. E. BLOOM. Studies on norepinephrine-containing afferents to Purkinje cells of rat cerebellum. 3. Evidence for mediation of norepinephrine effects by cyclic 3′,5′-adenosine monophosphate. *Brain Res.* 25: 535–553, 1971.
691. SINHA, N. L., M. L. GUPTA, AND K. P. BHARGAVA. Effect of histamine and antihistaminics on central vasomotor loci. *Eur. J. Pharmacol.* 5: 235–238, 1969.
692. SLOTKIN, T. A., R. J. SLEPETIS, S. J. WEIGEL, AND W. L. WHITMORE. Effects of α-fluoromethylhistidine (FMH), an irreversible inhibitor of histidine decarboxylase, on development of brain histamine and catecholamine systems in the neonatal rat. *Life Sci.* 32: 2997–2903, 1983.
693. SMITH, I. R., M. T. CLEVERLEY, C. R. GANELLIN, AND K. M. METTERS. Binding of [^{3}H]cimetidine to rat brain tissue. *Agents Actions* 10: 422–426, 1980.
694. SMITH, I. R., B. K. LEIGH, AND M. E. MYLEK. [^{3}H]-tiotidine binding to guinea-pig cortical and striatal membranes. *Agents Actions* 19: 169–173, 1986.
695. SMITS, R. P. J. M., H. W. M. STEINBUSCH, AND A. H. MULDER. Studies on the specificity of uptake and release of radiolabelled histamine in rat brain slices. *Neurochem. Int.* 12: 193–201, 1988.
695a. SNIDER, R. M., M. MCKINNEY, C. FORRAY, AND E. RICHELSON. Neurotransmitter receptors mediate cyclic GMP formation by involvement of arachidonic acid and lipoxygenase. *Proc. Natl. Acad. Sci. USA* 81: 3905–3909, 1984.
696. SNYDER, S. H. Tricyclic antidepressant drug interactions with histamine and α-adrenergic receptors. *Pharmakopsychiatr. Neuro-Psychopharmakol.* 13: 62–67, 1980.
697. SNYDER, S. H., B. BROWN, AND M. J. KUHAR. The subsynaptosomal localization of histamine, histidine decarboxylase and histamine methyltransferase in rat hypothalamus. *J. Neurochem.* 23: 37–45, 1974.
698. SNYDER, S. H., J. GLOWINSKI, AND J. AXELROD. The physiologic disposition of ^{3}H-histamine in rat brain. *J. Pharmacol. Exp. Ther.* 153: 8–14, 1966.
699. SPERK, G., H. HORTNAGL, H. REITHER, AND O. HORNYKIEWICZ. Evidence for neuronal localization of histamine-N-methyl-transferase in rat brain. *J. Neurochem.* 37: 525–526, 1981.
700. STAINES, W. M. A., T. YAMAMOTO, P. E. DADDONA, AND J. I. NAGY. Neuronal colocalisation of adenosine deaminase, monoamine oxidase, galanin and 5-hydroxytryptophan uptake in the tuberomammillary nucleus of the rat. *Brain Res. Bull.* 17: 351–365, 1986.
701. STAINES, W. M. A., T. YAMAMOTO, P. E. DADDONA, AND J. I. NAGY. The hypothalamus receives major projections from the tuberomammillary nucleus in rat. *Neurosci. Lett.* 76: 257–262, 1987.
702. STEAD, R. H., M. TOMIOKA, G. QUINONEZ, G. T. SIMON, S. Y. FELTEN, AND J. BIENENSTOCK. Intestinal mucosal mast cells in normal and nematode-infected rat intestines are in intimate contact with peptidergic nerves. *Proc. Natl. Acad. Sci. USA* 84: 2975–2979, 1987.
703. STEIN, C., AND D. WEINREICH. An in vitro characterization of γ-glutamylhistamine synthetase: a novel enzyme catalyzing histamine metabolism in the central nervous system of the marine mollusk, *Aplysia californica*. *J. Neurochem.* 38: 204–214, 1982.
704. STEINBERG, G. H., J. G. EPPEL, M. KANDEL, S. I. KANDEL, AND J. W. WELLS. H_2 histaminic receptors in rat cerebral cortex. 1. Binding of [^{3}H]histamine. *Biochemistry* 24: 6095–6107, 1985.
705. STEINBERG, G. H., M. KANDEL, S. I. KANDEL, AND J. W. WELLS. H_2 histaminic receptors in rat cerebral cortex. 2. Inhibition of [^{3}H]histamine by H_2 antagonists. *Biochemistry* 24: 6107–6115, 1985.
706. STEINBERG, G. H., M. KANDEL, S. I. KANDEL, AND J. W.

WELLS. H_2 histaminic receptors in rat cerebral cortex. 3. Inhibition of [^{3}H]histamine by H_2 agonists. *Biochemistry* 24: 6115–6125, 1985.

707. STEINBUSCH, H. W. M., AND A. H. MULDER. Immunohistochemical localization of histamine in neurons and mast cells in the rat brain. In: *Handbook of Chemical Neuroanatomy. Classical Transmitters and Transmitter Receptors in the CNS*, edited by A. Björklund, T. Hökfelt, and M. J. Kuhar. Amsterdam: Elsevier, 1984, vol. 3, pt. II, p. 126–140.

708. STEINBUSCH, H. W. M., AND A. H. MULDER. Localization and projections of histamine-immunoreactive neurons in the central nervous system of the rat. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 119–130.

709. STEINBUSCH, H. W. M., Y. SAUREN, H. GROENEWEGEN, T. WATANABE, AND A. H. MULDER. Histaminergic projections from the premammillary and posterior hypothalamic region to the caudate-putamen complex in the rat. *Brain Res.* 368: 389–393, 1986.

710. STEINBUSCH, H. W. M., AND A. A. J. VERHOFSTAD. Immunocytochemical demonstration of noradrenaline, serotonin and histamine and some observations on the innervation of the intracerebral blood vessels. In: *Neural Regulation of Brain Circulation*, edited by C. Owinan and J. E. Hardebo. Amsterdam: Elsevier, 1986, p. 181–194.

711. STERK, G. J., M. W. G. VAN DER SCHAAR, B. RADEMAKER, H. VAN DER GOOT, AND H. TIMMERMAN. Histamine H_2-binding on guinea-pig cerebral cortex. *Agents Actions* 18: 231–234, 1986.

712. STUDY, R. E., AND P. GREENGARD. Regulation by histamine of cyclic nucleotide levels in sympathetic ganglia. *J. Pharmacol. Exp. Ther.* 207: 767–778, 1978.

713. STURROCK, R. R. A morphological lifespan study of neurolipomastocytes in various regions of the mouse forebrain. *Neuropathol. Appl. Neurobiol.* 6: 211–219, 1980.

714. STÜTTGEN, G., AND W. JACOB. Die H-Substanzen des menschlichen Liquors. *Nervenarzt* 23: 60–63, 1952.

715. SUBRAMANIAN, N. Electrically induced release of radiolabeled histamine from rat hippocampal slices: opposing roles for H_1- AND H_2-receptors. *Life Sci.* 31: 557–562, 1982.

716. SUBRAMANIAN, N., AND A. H. MULDER. Potassium-induced release of tritiated histamine from rat brain tissue slices. *Eur. J. Pharmacol.* 35: 203–206, 1976.

717. SUBRAMANIAN, N., AND A. H. MULDER. Modulation by histamine of the efflux of radiolabeled catecholamines from rat brain slices. *Eur. J. Pharmacol.* 43: 143–152, 1977.

718. SUBRAMANIAN, N., AND T. A. SLOTKIN. Solubilization of a [^{3}H]cimetidine binding site from rat brain: a clonidine-sensitive H_2 receptor subtype? *Mol. Pharmacol.* 20: 240–243, 1981.

719. SUBRAMANIAN, N., W. L. WHITMORE, F. J. SEIDLER, AND T. A. SLOTKIN. Histamine stimulates brain phospholipid turnover through a direct H-1 receptor-mediated mechanism. *Life Sci.* 27: 1315–1319, 1980.

720. SUBRAMANIAN, N., W. L. WHITMORE, F. J. SEIDLER, AND T. A. SLOTKIN. Ontogeny of histaminergic neurotransmission in the rat brain: concomitant development of neuronal histamine, H-1 receptors AND H-1 receptor-mediated stimulation of phospholipid turnover. *J. Neurochem.* 36: 1137–1141, 1981.

721. SWAHN, C. G. Determinaton of 1-methylimidazole-4-acetic acid in brain tissue from rat AND mouse. *J. Neurochem.* 43: 830–834, 1984.

722. SWAHN, C. G., AND G. SEDVALL. Identification and determination of 1-methylimidazole-4-acetic acid in human cerebrospinal fluid by gas chromatography-mass spectrometry. *J. Neurochem.* 40: 688–696, 1983.

723. SWAHN, C. G., AND G. SEDVALL. Histamine metabolites in cerebrospinal fluid, the rationale for studying them and analytical aspects. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 197–202.

724. SWANSON, L. W. The projections from the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescent study in the rat. *Brain Res. Bull.* 9: 321–353, 1982.

725. SWANSON, L. W. The hypothalamus. In: *Handbook of Chemical Neuroanatomy. Integrated Systems of the CNS. Hypothalamus, Hippocampus, Amygdala, Retina*, edited by A. Björklund, T. Hökfelt, and L. W. Swanson. Amsterdam: Elsevier, 1987, vol. 5, pt. I, p. 1–124.

726. SWEATMAN, P., AND R. M. JELL. Dopamine and histamine sensitivity of rostral hypothalamic neurones in the cat: possible involvement in thermoregulation. *Brain Res.* 127: 173–178, 1977.

727. SWETT, C. P., AND J. A. HOBSON. The effects of posterior hypothalamic lesions on behavioral and electrographic manifestations of sleep in cats. *Arch. Ital. Biol.* 106: 279–283, 1968.

728. SZTRIHA, L., P. JOO, AND P. SZERDAHELYI. Histamine H_2-receptors participate in the formation of brain edema induced by kainic acid in rat thalamus. *Neurosci. Lett.* 75: 334–338, 1987.

729. TAGAMI, H., A. SUNAMI, M. AKAGI, AND T. TASAKA. Effect of histamine on the hippocampal neurons in guinea-pigs. *Agents Actions* 14: 538–542, 1984.

730. TAGO, H., H. KIMURA, AND T. MAEDA. MAO positive neurons projecting to neocortex from ventrocaudal hypothalamus in the rat. *Acta Anat. Nippon* 58: 243, 1983.

731. TAGUCHI, Y., T. WATANABE, H. KUBOTA, H. HAYASHI, and H. WADA. Purification of histidine decarboxylase from the liver of fetal rats and its immunochemical and immunohistochemical characterization. *J. Biol. Chem.* 259: 5214–5221, 1984.

732. TAGUCHI, Y., T. WATANABE, S. SHIOSAKA, M. TOHYAMA, and H. WADA. Immunohistochemical analysis of the cross-reaction of anti-rat histidine decarboxylase antibody with guinea-pig DOPA-decarboxylase. *Brain Res.* 340: 235–242, 1985.

733. TAKADA, M., Z. K. LI, AND T. HATTORI. A direct projection from the tuberomammillary nucleus to the spinal cord in the rat. *Neurosci. Lett.* 79: 257–262, 1987.

734. TAKEDA, N., S. INAGAKI, S. SHIOSAKA, Y. TAGUCHI, W. H. OERTEL, M. TOHYAMA, T. WATANABE, AND H. WADA. Immunohistochemical evidence for the coexistence of histidine decarboxylase-like and glutamate decarboxylase-like immunoreactivities in nerve cells of the magnocellular nucleus of the posterior hypothalamus of rats. *Proc. Natl. Acad. Sci. USA* 81: 7647–7650, 1984.

735. TAKEDA, N., S. INAGAKI, Y. TAGUCHI, M. TOHYAMA, T. WATANABE, AND H. WADA. Origins of histamine-containing fibers in the cerebral cortex of rats studied by immunohistochemistry with histidine decarboxylase as a marker and transection. *Brain Res.* 323: 55–63, 1984.

736. TAKEDA, N., M. MORITA, T. KUBO, A. YAMATODANI, T. WATANABE, H. WADA, AND T. MATSUNAGA. Histaminergic mechanism of motion sickness. *Acta Oto-Laryngol.* 101: 416–421, 1986.

737. TAMURA, K., J. M. PALMER, AND J. D. WOOD. Presynaptic inhibition produced by histamine at nicotinic synapses in enteric ganglia. *Neuroscience* 26: 171–179, 1988.

738. TAYLOR, J. E., AND E. RICHELSON. Desensitization of histamine H_1 receptor-mediated cyclic GMP formation in mouse neuroblastoma cells. *Mol. Pharmacol.* 15: 462–471, 1979.

739. TAYLOR, J. E., AND E. RICHELSON. High-affinity binding of [^{3}H]doxepin to histamine H_1-receptors in rat brain: possible identification of a subclass of histamine H_1-receptors. *Eur. J. Pharmacol.* 78: 279–285, 1982.

740. TAYLOR, K. M. Brain histamine. In: *Handbook of Psychopharmacology. Handbook of Biogenic Amines*, edited by L. L. Iversen, S. D. Iversen, and S. H. Snyder. New York: Plenum, 1976, vol. 3, p. 327–379.

741. TAYLOR, K. M., E. GFELLER, AND S. H. SNYDER. Regional localization of histamine and histidine in the brain of the rhesus monkey. *Brain Res.* 41: 171–179, 1972.

742. TAYLOR, K. M., AND R. LAVERTY. The interaction of chlordiazepoxide diazepam and nitrazepam with catecholamines and histamine in regions of the rat brain. In: *The Benzodiazepines*, edited by S. Garattini. New York: Raven, 1973, p. 191–201.

743. TAYLOR, K. M., AND S. H. SNYDER. Histamine in rat brain: sensitive assay of endogenous levels, formation in vivo and lowering by inhibitors of histidine decarboxylase. *J. Pharmacol. Exp. Ther.* 179: 619–633, 1971.

744. TAYLOR, K. M., AND S. H. SNYDER. Brain histamine: rapid

apparent turnover altered by restraint and cold stress. *Science Wash. DC* 172: 1037–1039, 1971.

745. TAYLOR, K. M., AND S. H. SNYDER. Dynamics of the regulation of histamine levels in mouse brain. *J. Neurochem.* 19: 841–854, 1972.

746. TAYLOR, K. M., AND S. H. SNYDER. Histamine methyltransferase: inhibition and potentiation by antihistamines. *Mol. Pharmacol.* 8: 300–310, 1972.

747. TAYLOR, K. M., AND S. H. SNYDER. The release of histamine from tissue slices of rat hypothalamus. *J. Neurochem.* 21: 1215–1223, 1973.

747a. THEOHARIDES, T. C. Mast cells: the immune gate to brain. *Life Sci.* 46: 607–617, 1990.

748. TRITHAPANDIDA, A., AND V. H. COHN. Brain histamine *N*-methyltransferase purification, mechanism of action, and inhibition by drugs. *Biochem. Pharmacol.* 27: 263–271, 1978.

749. TILLEMENT, J. P., M. GUERNET, A. DIEHL, I. BLANCO, M. BLANCO, AND J. R. BOISSIER. Variations en fonction de l'âge des taux cérébraux d'histamine et de L-histidine chez le rat. *J. Pharmacol. Paris* 2: 1–10, 1971.

750. TINDALL, G. T., AND J. C. GREENFIELD, JR. The effects of intraarterial histamine in blood flow in the internal and external carotid artery of man. *Stroke* 4: 46–49, 1973.

751. TOLEDO, A., J. SABRIA, R. RODRIGUEZ, R. BRANDNER, J. RODRIGUEZ, J. M. PALACIOS, AND I. BLANCO. Properties and ontogenic development of membrane-bound histidine decarboxylase from rat brain. *J. Neurochem.* 51: 1400–1406, 1988.

752. TÖLL, L., AND S. H. SNYDER. Solubilization and characterization of histamine H_1 receptors in brain. *J. Biol. Chem.* 257: 13593–13601, 1982.

753. TÖLL, L., V. T. TRAN, M. GAVISH, AND S. H. SNYDER. Properties of soluble histamine H_1-receptors in the brain. In: *Psychopharmacology and Biochemistry of Neurotransmitter Receptors*, edited by H. I. Yamamura, R. W. Olsen, and E. Usdin. Amsterdam: Elsevier, 1980, p. 301–311.

754. TOLONE, G., L. BONASERA, AND G. M. PONTIERI. Histamine binding to H_2-receptors stimulates phospholipid methylation in mast cells. *Experientia Basel* 38: 966–968, 1982.

754a. TRAIFFORT, E., M. RUAT, J. C. SCHWARTZ, J. HIRSCHFELD, AND W. SCHUNACK. Interaction of antidepressant drugs with guinea pig histamine H_2-receptors studied with [^{125}I]iodoaminopotentidine, a high affinity and selective ligand. *Eur. J. Pharmacol.* 183: 2053, 1990.

755. TRAN, V. T., R. S. L. CHANG, AND S. H. SNYDER. Histamine H_1-receptors identified in mammalian brain membranes with [^{3}H]mepyramine. *Proc. Natl. Acad. Sci. USA* 75: 6290–6294, 1978.

756. TRAN, V. T., A. D. FREEMAN, R. S. L. CHANG, AND S. H. SNYDER. Ontogenetic development of histamine H_1-receptor binding in rat brain. *J. Neurochem.* 34: 1609–1613, 1980.

757. TRAN, V. T., R. LEBOVITZ, L. TOLL, AND S. H. SNYDER. [^{3}H]doxepin interactions with histamine H_1-receptors and other sites in guinea pig and rat brain homogenates. *Eur. J. Pharmacol.* 70: 501–509, 1981.

758. TRAN, V. T., AND S. H. SNYDER. Histidine decarboxylase. Purification from fetal rat liver, immunologic properties and histochemical localization in brain and stomach. *J. Biol. Chem.* 256: 680–686, 1981.

759. TREHERNE, J. M., AND J. M. YOUNG. [^{3}H]-(+)-*N*-methyl-4-methyldiphenhydramine, a quaternary radioligand for the histamine H_1-receptor. *Br. J. Pharmacol.* 94: 797–810, 1988.

760. TREHERNE, J. M., AND J. M. YOUNG. Temperature-dependence of the kinetics of the binding of [^{3}H]-(+)-*N*-methyl-4-methyldiphenhydramine to the histamine H_1-receptor: comparison with the kinetics of [^{3}H]-mepyramine. *Br. J. Pharmacol.* 94: 811–822, 1988.

761. TRENDELENBURG, U. Stimulation of sympathetic centers by histamine. *Circ. Res.* 5: 105–110, 1957.

762. TRZECIAKOWSKI, J. P. Inhibition of guinea-pig ileum contractions mediated by a class of histamine receptor resembling the H_2 subtype. *J. Pharmacol. Exp. Ther.* 243: 874–880, 1987.

763. TUNG, A. S., J. T. BLAKE, I. J. ROMAN, P. H. VLASSES, R. K. FERGUSSON, AND H. J. ZWEERINK. In vivo and in vitro inhibition of human histidine decarboxylase by (*S*)-α-fluoromethylhistidine. *Biochem. Pharmacol.* 34: 3509–3515, 1985.

764. TUOMINEN, R. K. Attempts to antagonize the effect of histamine on the cold-stimulated thyrotropin secretion in male rats. *Acta Pharmacol. Toxicol.* 57: 371–377, 1985.

765. TUOMINEN, R. K. *Histamine in the Regulation of Thyrotropin Secretion in Rats* (PhD thesis). Helsinki: Univ. of Helsinki, 1986.

766. TUOMINEN, R. K., AND P. T. MÄNNISTÖ. Adrenalectomy modifies the effects of intracerebral histamine on the cold-stimulated TSH secretion in male rats. *Agents Actions* 18: 479–484, 1986.

767. TUOMINEN, R. K., AND P. T. MÄNNISTÖ. Thyrotropin release from superfused rat anterior pituitary cells is not affected by histamine. *Neuroendocrinol. Lett.* 8: 69–78, 1986.

768. TUOMINEN, R. K., P. T. MÄNNISTÖ, AND J. MATTILA. Studies on the site and mechanism of the inhibitory actions of intracerebral histamine on the cold-stimulated TSH secretion in male rats. *Brain Res.* 343: 329–335, 1985.

769. TUOMINEN, R. K., J. MATTILA, AND P. T. MÄNNISTÖ. Inhibition of the TSH secretion by histamine in male rats. *Acta Endocrinol.* 103: 88–94, 1983.

770. TUOMISTO, J., AND P. MÄNNISTÖ. Neurotransmitter regulation of anterior pituitary hormones. *Pharmacol. Rev.* 37: 249–332, 1985.

771. TUOMISTO, L. Ontogenesis and regional distribution of histamine-*N*-methyltransferase in the guinea pig brain. *J. Neurochem.* 28: 271–276, 1977.

772. TUOMISTO, L., AND L. ERIKSSON. Central antidiuretic effect of histamine (H) in the unanesthetized goat; effects of H_1 and H_2 antagonists. *J. Pharmacol.* 5: 101, 1974.

773. TUOMISTO, L., AND L. ERIKSSON. Antidiuresis induced by infusions of histamine into the brain ventricles of conscious hydrated goats. *Eur. J. Pharmacol.* 54: 191–201, 1979.

774. TUOMISTO, L., AND L. ERIKSSON. Cardiovascular and behavioural changes after i.c.v. infusions of histamine and agonists in conscious goats. *Agents Actions* 10: 165–166, 1980.

775. TUOMISTO, L., L. ERIKSSON, AND F. FYHRQUIST. Vasopressin release by histamine in the conscious goat. *Eur. J. Pharmacol.* 63: 19–24, 1980.

776. TUOMISTO, L., L. ERIKSSON, AND F. FYHRQUIST. Plasma vasopressin levels after I.C.V. infusion of histamine agonists in the conscious goat. *Agents Actions* 14: 553–560, 1984.

776a. TUOMISTO, L., H. KILPELAINEN, AND P. RIEKKINEN. Histamine and histamine-*N*-methyltransferase in the CSF of patients with multiple sclerosis. *Agents Actions* 13: 256–257, 1983.

777. TUOMISTO, L., AND J. TUOMISTO. Diurnal variations in brain and pituitary histamine and histamine-*N*-methyltransferase in the rat and guinea pig. *Med. Biol.* 60: 204–209, 1982.

778. TUOMISTO, L., J. TUOMISTO, AND E. J. WALASZEK. Uptake of histamine by rabbit hypothalamic slices. *Med. Biol.* 53: 40–46, 1975.

779. TUOMISTO, L., A. YAMATODANI, H. DIETL, U. WALDMANN, AND A. PHILIPPU. In vivo release of endogenous catecholamines, histamine and GABA in the hypothalamus of Wistar Kyoto and spontaneously hypertensive rats. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 323: 183–187, 1983.

780. UPRICHARD, D. C., D. A. GREENBERG, P. P. SHEEHAN, AND S. H. SNYDER. Tricyclic antidepressants: therapeutic properties and affinity for α-noradrenergic receptor binding sites in the brain. *Science Wash. DC* 199: 197–198, 1978.

781. VAN DER VLIET, A., J. P. VAN DER WERF, A. BAST, AND H. TIMMERMAN. Frequency-dependent autoinhibition of histamine release from rat cortical slices: a possible role for H_2 receptor reserve. *J. Pharm. Pharmacol.* 40: 577–579, 1988.

782. VAN DER WERF, J. F., A. BAST, G. J. BIJLOO, A. VAN DER VLIET, AND H. TIMMERMAN. HA autoreceptor assay with superfused slices of rat brain cortex and electrical stimulation. *Eur. J. Pharmacol.* 138: 199–206, 1987.

783. VAN DER WERF, J. F., G. J. BIJLOO, A. VAN DER VLIET, A. BAST, AND H. TIMMERMAN. H_2 receptor assay in electrically-stimulated superfused slices of rat brain cortex; effects of *N*-alkylated histamines and impromidine analogues. *Agents Actions* 20: 239–243, 1987.

784. VANNI-MERCIER, G., K. SAKAI, AND M. JOUVET. Neurones spécifiques de l'éveil dans l'hypothalamus postérieur du chat. *C. R. Hebd. Seances Acad. Sci.* 298: 195–200, 1984.

785. VERBURG, K. M., R. R. BOWSHER, R. L. ZERBE, AND D. P.

HENRY. The effect of hypertonic saline administration or stalk transection on histamine and histamine *N*-methyltransferase in the rat posterior pituitary. *Agents Actions* 18: 494–498, 1986.

786. VERBURG, K. M., AND D. P. HENRY. Histamine *N*-methyltransferase-enzymology and functional aspects. In: *Neuromediate, Neurotransmitter Enzymes*, edited by A. A. Boulton, G. B. Baker, and P. H. Yu. Clifton, NJ: Humana, 1986, p. 147–205.
787. VERDIERE, M., C. ROSE, AND J. C. SCHWARTZ. Synthesis and release of [^{3}H]-histamine in slices from rat brain. *Agents Actions* 4: 184–185, 1974.
788. VERDIERE, M., C. ROSE, AND J. C. SCHWARTZ. Synthesis and release of histamine studied on slices from rat hypothalamus. *Eur. J. Pharmacol.* 31: 157–168, 1975.
789. VERDIERE, M., C. ROSE, AND J. C. SCHWARTZ. Turnover of cerebral histamine in a stressful situation. *Brain Res.* 129: 107–119, 1977.
790. VERVERKEN, D., P. VAN VELDHOVEN, C. PROOST, H. CARTON, AND H. DE WULF. On the role of calcium ions in the regulation of glycogenolysis in mouse brain cortical slices. *J. Neurochem.* 38: 1286–1295, 1982.
791. VINCENT, S. R., T. HÖKFELT, L. A. SKIRBOLL, AND J. Y. WU. Hypothalamic γ-aminobutyric acid neurons project to the neocortex. *Science Wash. DC* 220: 1309–1311, 1983.

791a. VON ECONOMO, C. Die Pathologie des Schlafes. In: *Handbuch der Normalen und Pathologischen Psychologie*, edited by A. Berthe, G. von Bergmann, G. Embden, and A. Ellinger. Berlin: Springer-Verlag, 1926, vol. 17, p. 591–610.

792. WADA, H., T. WATANABE, K. MAEYAMA, Y. TAGUCHI, AND H. HAYASHI. Mammalian histidine decarboxylase and its suicide substrate α-fluoromethylhistidine. In: *Chemical and Biological Aspects of Vitamin B_6 Catalysis*, edited by A. E. Evangelopoulos. New York: Liss, 1984, pt. A, p. 245–254.
793. WADA, H., T. WATANABE, A. YAMATODANI, K. MAEYAMA, N. ITOI, R. CACABELOS, M. SEO, S. KIYONO, K. NAGAI, AND H. NAKAGAWA. Physiological functions of histamine in the brain. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 225–236.
794. WAHL, M., AND W. KUSCHINSKY. The dilating effect of histamine on pial arteries of cats and its mediation by H_2 receptors. *Circ. Res.* 44: 161–165, 1979.
795. WAHLESTEDT, C., G. SKAGERBERG, R. HÅKANSON, T. SUNDLER, H. WADA, AND T. WATANABE. Spinal projections of hypothalamic histidine decarboxylase immunoreactive neurones. *Agents Actions* 16: 231–233, 1985.
796. WALDMEIER, P. C., J. J. FELDTRAUER, AND L. MAITRE. Methyl-histamine: evidence for selective deamination by MAO B in the rat brain in vivo. *J. Neurochem.* 29: 785–790, 1977.
797. WALLACE, R.M., AND J. M. YOUNG. Temperature dependence of the binding of [^{3}H] mepyramine and related compounds to the histamine H_1 receptor. *Mol. Pharmacol.* 23: 60–66, 1983.
798. WANG, N. P., H. FUKUI, H. MATSUOKA, AND H. WADA. Determination of the molecular size of the hepatic H_1-receptor by target size analysis. *Biochem. Biophys. Res. Commun.* 137: 593–598, 1986.
799. WANG, N. P., H. FUKUI, T. WATANABE, AND H. WADA. Solubilization and characterization of histamine H_1-receptor from guinea-pig brain. *Prog. Amines* 4: 7–17, 1987.
800. WARRANDER, S. E., D. B. NORRIS, T. J. RISING, AND T. P. WOOD. [^{3}H] cimetidine and the H_2-receptor. *Life Sci.* 33: 1119–1126, 1983.
801. WATANABE, T., H. NAKAMURA, L. Y. LIANG, A. YAMATODANI, AND H. WADA. Partial purification and characterization of L-histidine decarboxylase from fetal rats. *Biochem. Pharmacol.* 28: 1149–1155, 1979.
802. WATANABE, T., Y. TAGUCHI, H. HAYASHI, H. WADA, H. KUBOTA, Y. TERANO, J. TANAKA, S. SHIOSAKA, AND M. TOHYAMA. Evidence for the presence of a histaminergic neuron system in the rat brain: an immunochemical analysis. *Neurosci. Lett.* 39: 249–254, 1983.
803. WATANABE, T., Y. TAGUCHI, S. SHIOSAKA, J. TANAKA, H. KUBOTA, Y. TERANO, M. TOHYAMA, AND H. WADA. Distribution of the histaminergic neuron system in the central nervous system of rats: a fluorescent immunohistochemical analysis with histidine decarboxylase as a marker. *Brain Res.* 295: 13–26, 1984.
804. WATANABE, T., Y. TAGUCHI, N. TAKEDA, S. SHIOSAKA, M. TOYAMA, AND H. WADA. Purification of and antibodies against L-histidine decarboxylase. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 91–102.
805. WATANABE, T., AND H. WADA. Histidine decarboxylase and histamine-*N*-methyltransferase. In: *Methods in Biogenic Amine Research*, edited by S. Parvez, T. Nagatsu, I. Nagatsu, and H. Parvez. Amsterdam: Elsevier, 1983, p. 689–720.
806. WATANABE, T., M. YAMADA, Y. TAGUCHI, H KUBOTA, K. MAEYAMA, A. YAMATODANI, H. FUKUI, S. SHIOSAKA, M. TOHYAMA, AND H. WADA. Purification and properties of histidine decarboxylase isozymes and their pharmacological significance. In: *Advances in Histamine Research*, edited by B. Uvnas and K. Tasaka. Oxford, UK: Pergamon, 1982, p. 93–106.
807. WAUQUIER, A., AND C. J. E. NIEMEGEERS. Effects of chlorphenitramine, pyrilamine and astemizole on intracranial self-stimulation in rats. *Eur. J. Pharmacol.* 72: 245–248, 1981.
808. WAUQUIER, A., W. A. E. VAN DEN BROECK, F. AWOUTERS, AND P. A. J. JANSSEN. A comparison between astemizole and other antihistamines on sleep-wakefulness cycles in dogs. *Neuropharmacology* 20: 853–859, 1981.
809. WAUQUIER, A., W. A. E. VAN DEN BROECK, F. AWOUTERS, AND P. A. J. JANSSEN. Further studies on the distinctive sleep-wakefulness profiles of antihistamines (Astemizole, Ketotifen, Terfenadine) in dogs. *Drug Dev. Res.* 4: 617–625, 1984.
810. WEINER, R. I., AND W. F. GANONG. Role of brain monoamines and histamine in regulation of anterior pituitary secretion. *Physiol. Rev.* 58: 905–976, 1978.
811. WEINREICH, D. Neurobiology of a histaminergic neuron in the CNS of the mollusk *Aplysia californica*. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 205–214.
812. WEINREICH, D., AND L. RUBIN. Irreversible inhibitors of histidine decarboxylase in *Aplysia* ganglia: a tool for the identification of histaminergic synapses. *Comp. Biochem. Physiol.* 69: 383–385, 1981.
813. WEINREICH, D., AND Y. T. YU. The characterization of histidine decarboxylase and its distribution in nerves, ganglia and in single neuronal cell bodies from the CNS of *Aplysia californica*. *J. Neurochem.* 28: 361–369, 1977.
814. WELLS, J. W., D. L. CYBULSKY, M. KANDEL, S. I. KANDEL, AND G. H. STEINBERG. Cognitive properties of H_2-receptors revealed by [^{3}H]-histamine. In: *Frontiers in Histamine Research*, edited by C. R. Ganellin and J. C. Schwartz. Oxford, UK: Pergamon, 1985, p. 69–76.
815. WHITE, J. M. The discriminative stimulus properties of mepyramine. *Life Sci.* 37: 1145–1153, 1985.
816. WHITE, J. M., AND G. R. RUMBOLD. Behavioural effects of histamine and its antagonists: a review. *Psychopharmacology* 95: 1–14, 1988.
817. WHITE, T. Formation and catabolism of histamine in brain tissue in vitro. *J. Physiol. Lond.* 149: 34–42, 1959.
818. WHITE, T. Formation and catabolism of histamine in cat brain in vivo. *J. Physiol. Lond.* 152: 299–308, 1960.
819. WHITE, T. Peripheral vascular effects of histamine administered into the cerebral ventricles of anaesthetized cats. *Experientia Basel* 21: 132–133, 1965.
820. WIESNER-MENZEL, L., B. SCHULZ, F. VAKILZADEH, AND B. M. CZARNETZKI. Electron microscopical evidence for a direct contact between nerve fibers and mast cells. *Acta Dermatovenerol. Iugosl.* 61: 465–469, 1981.
821. WILCOX, B. J., AND V. S. SEYBOLD. Localization of neuronal histamine in rat brain. *Neurosci. Lett.* 29: 105–110, 1982.
822. WILLIAMS, R. G., AND G. J. DOCKRAY. Distribution of enkephalin-related peptides in rat brain. Immunohistochemical studies using antisera to Met^5-enkephalin and Met^5-enkephalin Arg^6-Phe^7. *Neuroscience* 9: 563–586, 1983.
823. WINTER, J. C. Sedation and the stimulus properties of antihistamines. *Pharmacol. Biochem. Behav.* 22: 15–17, 1985.
824. WOLF, P., AND M. MONNIER. Electroencephalograpic behav-

ioral and visceral effects of intraventricular infusion of histamine in the rabbit. *Agents Actions* 3: 196, 1973.

825. WOUTERLOOD, F. G. Ultrastructure of histaminergic neurons in rat brain: immuno-electron-microscopy and Golgi-electron-microscopy. In: *Monoaminergic Neurons: Light Microscopy and Ultrastructure*, edited by H. W. M. Steinbusch. New York: Wiley, 1987, p. 315–338.

826. WOUTERLOOD, F. G., J. G. J. M. BOL, AND H. W. M. STEINBUSCH. Double-label immunocytochemistry: combination of anterograde neuroanatomical tracing with phaseolus vulgaris leucoagglutinin and enzyme immunocytochemistry of target neurons. *J. Histochem. Cytochem.* 35: 817–823, 1987.

827. WOUTERLOOD, F. G., AND R. P. A. GAYKEMA. Innervation of histaminergic neurons in the posterior hypothalamic region by medial preoptic neurons. Anterograde tracing with phaseolus vulgaris leucoagglutinin combined with immunocytochemistry of histidine decarboxylase in the rat. *Brain Res.* 455: 170–176, 1988.

828. WOUTERLOOD, F. G., R. P. A. GAYKEMA, H. W. M. STEINBUSCH, T. WATANABE, AND H. WADA. The connections between the septum-diagonal band complex and histaminergic neurons in the posterior hypothalamus of the rat. Anterograde tracing with *Phaseolus vulgaris*-leucoagglutinin combined with immunocytochemistry of histidine decarboxylase. *Neuroscience* 26: 827–845, 1988.

829. WOUTERLOOD, F. G., Y. M. H. F. SAUREN, AND H. W. M. STEINBUSCH. Histaminergic neurons in the rat brain: correlative immunocytochemistry, golgi impregnation and electron microscopy. *J. Comp. Neurol.* 252: 227–244, 1986.

830. WOUTERLOOD, F. G., H. W. M. STEINBUSCH, P. G. M. LUITEN, AND J. G. J. M. BOL. Projection from the prefrontal cortex to histaminergic cell groups in the posterior hypothalamic region of the rat. Anterograde tracing with phaseolus vulgaris leucoagglutinin combined with immunocytochemistry of histidine decarboxylase. *Brain Res.* 406: 330–336, 1987.

831. XU, J., AND D. M. CHUANG. Serotonergic, adrenergic and histamincrgic receptors coupled to phospholipase C in cultured cerebellar granule cells of rats. *Biochem. Pharmacol.* 14: 2353–2358, 1987.

832. YAMADA, M., T. WATANABE, H. FUKUI, Y. TAGUCHI, AND H. WADA. Comparison of histidine decarboxylase from rat stomach and brain with that from whole bodies of rat fetus. *Agents Actions* 14: 143–152, 1984.

833. YAMATODANI, A., K. MAEYAMA, T. WATANABE, H. WADA, AND Y. KITAMURA. Tissue distribution of histamine in a mutant mouse deficient in mast cells: clear evidence for the presence of non-mast cell histamine. *Biochem. Pharmacol.* 31: 305–310, 1982.

834. YERAMIAN, E., M. GARRARG, AND J. C. SCHWARTZ. *N*-ethylmaleimide-induced changes in agonist affinity for histamine H_1-receptors in the guinea pig brain. *Mol. Pharmacol.* 28: 155–162, 1985.

835. YOSHITOMI, I., Y. ITOH, R. OISHI, AND K. SAEKI. Brain histamine turnover enhanced by footshock. *Brain Res.* 362: 195–198, 1986.

836. YOUNG, A. B., C. D. PERT, D. G. BROWN, K. M. TAYLOR, AND S. H. SNYDER. Nuclear localization of histamine in neonatal rat brain. *Science Wash. DC* 173: 247–249, 1971.

836a. YOUNG, C. S., R. MASON, AND S. J. HILL. Studies on the mechanism of histamine-induced release of noradrenaline and 5-hydroxytryptamine from slices of rat cerebral cortex. *Biochem. Pharmacol.* 37: 2799–2805, 1988.

837. ZAPPIA, V., C. R. ZYDEK-CWICK, AND F. SCHLENK. The specificity of *S*-adenonylmethionine derivatives in methyl transfer reactions. *J. Biol. Chem.* 244: 4499–4503, 1969.

838. ZAWILSKA, J., AND J. Z. NOWAK. Changes in the rat brain histamine content following metoprine and other histamine-methyl-transferase (HMT) inhibitors. *J. Pharmacol.* 37: 809–818, 1985.

ELSEVIER

European Neuropsychopharmacology 14 (2004) 332–336

EUROPEAN NEURO-PSYCHOPHARMACOLOGY

www.elsevier.com/locate/euroneuro

The effect of famotidine addition on olanzapine-induced weight gain in first-episode schizophrenia patients: a double-blind placebo-controlled pilot study

Michael Poyurovsky[a,b,*], Vered Tal[a], Rachel Maayan[d], Irit Gil-Ad[d], Camil Fuchs[c], Abraham Weizman[d]

[a] *Research Unit, Tirat Carmel Mental Health Center, 9 Eshkol Street, 30200 Tirat Carmel, Israel*
[b] *Rappaport Faculty of Medicine, Israel Institute of Technology-Technion, Haifa, Israel*
[c] *Department of Statistics and Operations Research, Laboratory of Biological Psychiatry, Tel Aviv University, Tel Aviv, Israel*
[d] *Felsenstein Medical Research Center, Geha Mental Health Center, Petah Tiqva, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

Received 2 May 2003; accepted 16 October 2003

Abstract

Olanzapine treatment is associated with substantial weight gain. In this double-blind placebo-controlled study we evaluated whether the H2 antagonist famotidine may prevent/attenuate olanzapine-induced weight gain. Fourteen first-episode DSM-IV schizophrenia patients were randomly allocated to receive either famotidine (40 mg/day, $n=7$) or placebo ($n=7$) in addition to olanzapine (10 mg/day) for 6 weeks. All patients completed the trial. Patients in both groups showed a similar increase in body weight (olanzapine/famotidine: 4.8 (3.2) kg and olanzapine/placebo: 4.9 (1.6) kg, respectively; a between-group difference of 0.14 (1.3) kg). Four of seven (57.1%) patients in the olanzapine/famotidine group and three of seven (42.9%) in the olanzapine/placebo group gained at least 7% of their initial body weight, a cut-off for clinically significant weight gain. Famotidine addition was safe and well tolerated and did not interfere with olanzapine's therapeutic effect. In conclusion, famotidine (40 mg/day for 6 weeks) is not effective in preventing/attenuating weight gain in olanzapine-treated first-episode schizophrenia patients.

Keywords: Olanzapine; Histamine H2 antagonist; Weight gain; Famotidine; Schizophrenia

1. Introduction

Atypical antipsychotic agents, primarily olanzapine and clozapine, have been associated with significant weight gain (Allison et al., 1999). The mechanism underlying weight gain induced by atypical antipsychotics has not been clarified, though serotonergic, noradrenergic and histaminergic systems have been implicated (Baptista et al., 2002). Within the histaminergic system, the histamine H2 receptor appeared to be one of the possible mediators of feeding behavior and weight regulation (Doi et al., 1994). It was shown that H2 antagonists (cimetidine, ranitidine, famotidine) attenuated weight gain in rats (Stoa-Birketvedt et al., 1997), and cimetidine reduced weight in obese humans (Stoa-Birketvedt, 1993; Stoa-Birketvedt et al., 1998). Administration of the H2 antagonist nizatidine was associated with weight reduction in some olanzapine-treated schizophrenia patients (Sacchetti et al., 2000; Cavazzoni et al., 2003).

As part of our ongoing project aimed to evaluate the preventing/attenuating weight gain potential of pharmacological agents exerting selective effect at serotonergic, noradrenergic and histaminergic systems (Poyurovsky et al., 2002, 2003), we sought to determine whether famotidine may be effective in limiting weight gain in olanzapine-treated schizophrenia patients. Addition of famotidine to typical antipsychotics in schizophrenia patients had a beneficial adjunctive effect and was safe and well tolerated (Kaminsky et al., 1990; Rosse et al., 1996). To the best of our knowledge this is the first study evaluating the putative weight attenuating effect of famotidine in schizophrenia patients treated with the atypical antipsychotic olanzapine.

* Corresponding author. Tel.: +972-4-8559-349; fax: +972-4-8559-330.
E-mail address: tymichael@matat.health.gov.il (M. Poyurovsky).

0924-977X/$ - see front matter © 2003 Elsevier B.V./ECNP. All rights reserved.
doi:10.1016/j.euroneuro.2003.10.004

Since young and previously untreated patients seem to be particularly vulnerable to olanzapine-induced weight gain (Kinon et al., 2000; Potenza et al., 1999), we evaluated the effect of famotidine on weight gain in first-episode schizophrenia patients.

2. Experimental procedures

2.1. Patient sample

The study sample consisted of 14 patients (nine men, five women) hospitalized for a first-episode of acute psychosis at the Tirat Carmel Mental Health Center, Tirat Carmel (Israel). All met DSM-IV criteria for schizophrenic or schizophreniform disorder. The diagnosis was based on the Structured Clinical Interview for DSM-IV Axis-I Disorders, Patient Edition (SCID-P) (First et al., 1995). Exclusion criteria were: major mood disorders, substance-induced psychoses, medical illnesses that could affect body weight (e.g. diabetes mellitus, hypothyroidism) and patients who had body mass index (BMI) >30 kg/m^2. None of the study participants had abnormal findings on routine physical examination and laboratory tests. The study was approved by the Institutional Review Board. Written informed consent was obtained from all participants after they received a full explanation of the nature of the study.

2.2. Study design

A double-blind placebo-controlled randomized design was used. The participants were randomly allocated to receive either famotidine (40 mg/day at 08:00 h; $n=7$) or placebo (at 08:00 h; $n=7$) in addition to olanzapine (10 mg at 20:00 h) for 6 weeks. Administration of trihexyphenidyl (5–10 mg/day) for extrapyramidal side effects (EPS) and diazepam (5–10 mg/day) for insomnia or agitation were allowed on an as-needed basis. The doses of all medications remained unchanged during the entire study period. Meals were served three times a day, and patients were not placed on a special diet or special physical exercise program for weight reduction.

2.3. Assessments

Weight and BMI were measured at baseline and at weeks 1, 2, 4 and 6 at 08:00 h before meals. All weight measurements were performed by a research nurse blinded to the patients' treatment assignment. Clinical assessment instruments included the Clinical Global Impression (CGI) scale for severity of psychosis (Guy, 1976), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983). Drug-induced EPS were evaluated by the Simpson–Angus Scale (SAS) (Simpson and Angus, 1970). Other emergent drug-induced side effects were closely monitored. Clinical ratings were done at baseline and at the end of week 6 by the same trained psychiatrist (V.T.) who was blinded to the patients' treatment assignments.

2.4. Statistical analysis

Chi-square (χ^2) and Student's t-test were used as appropriate to evaluate between-group differences in baseline characteristics and changes of rating scale scores from baseline to endpoint. Between-group differences in body weight and BMI were analyzed using analysis of covariance with repeated measurements (ANCOVA-RM) with the baseline weight or BMI as covariates. The relationship between initial BMI and body weight changes at 6 weeks was assessed using Pearson's correlation. All tests were two-tailed; P-value less than 0.05 was considered significant. Results are presented as mean ± S.D.

3. Results

Prior to the initiation of olanzapine treatment all participants were treated during the current first admission by typical antipsychotic agents [haloperidol 5–10 mg/day ($n=10$) or perphenazine 8–16 mg/day ($n=4$)] for less than 4 weeks. The olanzapine/famotidine group did not differ in any of the demographic, clinical or weight characteristics from the olanzapine/placebo group at baseline (Table 1). Body mass indices were within the normal range (18.5–24.9 kg/m^2). All study patients completed the 6-week trial.

Patients in both groups revealed similar gradual increase in body weight and BMI (Table 2). ANCOVA-RM for weight and BMI found lack of significant group effect [weight: $F(1,11)=0.045$; $P=0.836$; BMI: $F(1,11)=0.059$; $P=0.81$]

Table 1
Baseline demographic, clinical and weight-related characteristics (mean ± S.D.) of first-episode schizophrenia patients treated with olanzapine/famotidine ($n=7$) or olanzapine/placebo ($n=7$)

Patient variables	Olanzapine/ famotidine	Olanzapine/ placebo	Statistics
Demographics	23.(1.4)	22.1 (1.9)	$t=1.23$ $P=0.24$
Age (years)	4:3	5:2	$\chi^2=0.31$ $P=0.58$
Gender (M:F)	2.9 (3.2)	2.2 (1.9)	$t=0.50$ $P=0.63$
Duration of illness (years)	12.3 (5.0)	13.1 (3.2)	$t=0.36$ $P=0.73$
Rating scale scores			
SAPS	8.6 (3.7)	7.7 (3.3)	$t=0.48$ $P=0.64$
SANS	12.0 (4.2)	12.3 (5.0)	$t=0.12$ $P=0.91$
CGI	5.0 (1.0)	4.6 (0.5)	$t=0.95$ $P=0.36$
SAS	13.4 (2.1)	13.4 (2.1)	$t=0.93$ $P=0.37$
Weight/BMI			
Weight (kg)	67.2 (7.7)	64.7 (6.5)	$t=0.66$ $P=0.52$
BMI (kg/m^2)	22.3 (2.0)	23.1 (3.3)	$t=0.55$ $P=0.59$

SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; CGI, Clinical Global Impression; SAS, Simpson–Angus Scale; BMI, body mass index.

Table 2
Body weight and BMI (mean ± S.D.) indices and changes from baseline in patients treated with olanzapine/famotidine ($n=7$) or olanzapine/placebo ($n=7$) for 6 weeks

	Olanzapine/famotidine				Olanzapine/placebo			
	Weight	Δ weight	BMI	Δ BMI	Weight	Δ weight	BMI	Δ BMI
Baseline	67.2 (7.7)		22.3 (2.0)		64.7 (6.5)		23.1 (3.3)	
Week 1	68.4 (8.6)	1.3 (1.3)	22.7 (2.3)	0.4 (0.4)	66.4 (5.5)	1.7 (1.7)	23.7 (3.1)	0.7 (0.3)
Week 2	69.1 (9.2)	2.0 (2.0)	22.9 (2.4)	0.6 (0.5)	67.1 (5.5)	2.4 (1.8)	23.9 (3.0)	0.9 (0.5)
Week 4	71.1 (9.9)	4.0 (2.8)	23.6 (2.5)	1.3 (0.7)	68.3 (5.8)	3.6 (1.1)	24.3 (3.1)	1.3 (0.3)
Week 6	72.0 (9.7)	4.8 (3.2)	23.9 (2.4)	1.6 (0.8)	69.6 (6.1)	4.9 (1.6)	24.8 (3.2)	1.7 (0.3)

Δ Weight and Δ BMI, difference from baseline.

The mean weight gain in the olanzapine–famotidine group was 4.8 (3.2) kg, and in the olanzapine–placebo group 4.9 (1.6) kg; a negligible difference of 0.14 (1.3) kg ($t=0.21$, $df=12$; $P=0.91$). Four of seven (57.1%) patients in the olanzapine/famotidine group and three of seven (42.9%) patients in the olanzapine/placebo group gained more than 7% of initial body weight, a cut-off for clinically significant weight gain ($\chi^2=0.29$; $df=1$, $P=0.59$). There was no correlation between baseline BMI and the increase in body weight at 6 weeks in either group (olanzapine/famotidine: $r=-0.03$, $df=6$, $P=0.91$; olanzapine/placebo: $r=0.12$, $df=6$, $P=0.72$).

There was a significant decrease in the CGI scores within each group from baseline to week 6 (olanzapine/famotidine 5.0(0.8) vs. 3.7(0.8), $t=3.04$, $=P<0.01$; olanzapine/placebo 4.6(0.4) vs. 3.6(0.8), $t=2.96$, $P<0.01$), and non-significant decrease in SAPS (olanzapine/famotidine 8.6(3.7) vs. 5.9(3.1), $t=1.48$, $P=0.16$; olanzapine/placebo 7.7(3.3) vs. 6.0(4.4), $t=0.82$, $P=0.43$) and SANS scores (olanzapine/famotidine 12.3(3.0) vs. 9.4(3.3), $t=1.17$, $P=0.11$; olanzapine/placebo 13.1(2.9) vs. 11.3(2.5), $t=1.24$, $P=0.24$). No between-group differences were found in changes from baseline in either CGI ($t=0.77$, $P=0.46$), SAPS ($t=0.64$; $P=0.54$) or SANS ($t=0.41$, $P=0.69$) scores.

There was a significant improvement of Parkinsonian symptoms from baseline to endpoint as measured by SAS, in both groups (olanzapine/famotidine 13.4(1.3) vs. 8.9(1.6), $t=5.76$, $P<0.01$; olanzapine/placebo 15.9(4.4) vs. 10.9(1.9), $t=2.76$, $P=0.02$), with no revealed between-group difference ($t=0.16$, $P=0.88$). Four of seven (57.1%) patients in the olanzapine/famotidine group and five of seven (71.4%) in the olanzapine/placebo group reported daytime somnolence ($\chi^2=0.31$, $df=1$, $P=0.58$).

4. Discussion

The results of the present study indicate that administration of olanzapine with either famotidine or placebo is associated with substantial weight gain in first-episode schizophrenia patients. Roughly half of the study participants exhibited clinically significant weight gain. These findings are consistent with our previous report demonstrating a similar magnitude of weight increase in first-episode schizophrenia patients treated with olanzapine and either fluoxetine or placebo (Poyurovsky et al., 2002). In addition, these findings substantiate earlier reports indicating that young and previously untreated schizophrenia patients are vulnerable to weight gain during the initial stages of olanzapine treatment (Kinon et al., 2000; Potenza et al., 1999).

The major finding of the present study is that the H2-antagonist famotidine (40 mg/day) co-administered with olanzapine was ineffective in attenuating weight gain in first-episode schizophrenia patients. Patients treated with the olanzapine/famotidine combination revealed an increase in body weight similar to their counterparts in the olanzapine/placebo group [4.8 (3.2) and 4.9 (1.6) kg, respectively], and no patients in either group maintained their initial weight. Noteworthy, similar to our previous reports (Poyurovsky et al., 2002, 2003) we found no significant correlation between initial BMI and change in body weight at the end of 6 weeks.

Although an initial report describing the potential of the H2-antagonist nizatidine (300 mg/day) to attenuate olanzapine-induced weight-gain was encouraging (Sacchetti et al., 2000), a subsequent controlled study demonstrated only an early transient effect of nizatidine (300 mg b.i.d.) in limiting olanzapine-induced weight gain that waned by week 16 of the trial (Cavazzoni et al., 2003). Overall, it seems that H2 antagonists (famotidine, nizatidine) are of limited value in prevention and/or attenuation of olanzapine-induced weight gain in schizophrenia patients.

In contrast to the positive effect of add-on famotidine on clinical ratings in chronic schizophrenia patients receiving typical antipsychotics (Rosse et al., 1996; Kaminsky et al., 1990), the addition of famotidine revealed no adjunctive clinical effect on both positive (SAPS) and negative (SANS) symptoms in our first-episode olanzapine-treated schizophrenia patients. The lack of effect of add-on famotidine on schizophrenia symptoms may be accounted for by the small sample size and short duration of treatment. Famotidine addition was safe and well tolerated by olanzapine-treated patients. No treatment-emergent EPS were reported. Moreover, olanzapine treatment with either famotidine or placebo was associated with a significant improvement of Parkinsonian symptoms induced by typical antipsychotics administered prior to olanzapine initiation.

The major limitations of the present study are small sample size, fixed doses of both famotidine and olanzapine

and short duration of trial. The absence of a significant between-group difference in weight gain may reflect a type II error. The slight attenuation of weight gain (0.14 kg) by famotidine might be a chance finding or a real effect, and the small sample size is insufficient to determine which is correct. According to power analysis with sample sizes, as in our study ($n=7$ in each group), we would have detected with a power of 80% only differences in means larger than 3.96 kg.

Several factors may account for famotidine's failure to attenuate olanzapine-induced weight gain. Olanzapine blood levels may be increased by add-on famotidine and thus counteract famotidine's putative weight reducing effect. However, this seems unlikely, since famotidine appears not to be metabolized by hepatic enzymes (Langtry et al., 1989) and no significant pharmacokinetic interactions between famotidine and antipsychotics have been reported (Prell et al., 1996). In addition, weight gain potential was reported not to correlate with olanzapine dose and/or blood levels (Kinon et al., 2000). It is also possible that higher famotidine doses may be required to affect both peripheral and central histaminergic mechanisms relevant to body weight regulation (Stoa-Birketvedt et al., 1997). Finally, there is increasing evidence that H1 rather than H2 antagonism may be pertinent to antipsychotic drug-induced weight gain. It was shown that H1-receptor antagonism increased feeding in rodents (Fukagawa et al., 1989), and H1-knockout mice are resistant to the anorectic effect of leptin and prone to obesity (Masaki et al., 2001). Recently, Kroeze et al. (2003) evaluated the relationship between receptor affinities profile of typical and atypical antipsychotics with their potential to induce weight gain and found that the most robust predictor of a drug's propensity to increase weight was its affinity for the H1-receptor. Noteworthy, antipsychotic agents (clozapine, olanzapine) and antidepressants (amitriptyline, mirtazapine) with the highest propensity to induce weight gain are potent H1-antagonists. Finally, other than histaminergic mechanisms (e.g. 5H2C, beta-adrenergic) are also involved in antipsychotic-induced weight gain (Baptista et al., 2002). Since weight gain appeared to be a risk factor for hyperlipidemia, diabetes mellitus and cardiovascular disease, a further search for effective pharmacological approaches for this common and potentially serious complication of antipsychotic drug treatment is warranted.

Acknowledgements

The authors acknowledge the assistance of Rena Kurs in preparation of the manuscript.

References

Allison, D.B., Mentore, J.L., Heo, M., Chandler, L.P., Cappelleri, J.C., Infante, M.C., Weiden, P.J., 1999. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am. J. Psychiatry 156, 1686–1696.

Andreasen, N.C., 1983. Scale for the Assessment of Negative Symptoms (SANS) The University of Iowa, Iowa City.

Andreasen, N.C., 1984. Scale for the Assessment of Positive Symptoms (SANS) The University of Iowa, Iowa City.

Baptista, T., Kin, N.M.K.N.Y., Beaulieu, S., de Baptista, E.A., 2002. Obesity and related metabolic abnormalities during antipsychotic drug administration: mechanisms, management and research perspective. Psychopharmacology 35, 205–219.

Cavazzoni, P., Tanaka, Y., Roychowdhury, S.M., Breier, A., Allison, D.B., 2003. Nizatidine for prevention of weight gain with olanzapine: a double-blind placebo-controlled study. Eur. Neuropsychopharmacol. 13, 81–85.

Doi, T., Sakata, T., Yoshimatsu, H., Machidori, H., Machidori, H., Kurokawa, M., Jayasekara, L.A., Niki, N., 1994. Hypothalamic neuronal histamine regulates feeding circadian rhythm in rats. Brain Res. 641, 11–18.

First, M.B., Spitzer, R.L., Gibbon, M., 1995. Structural Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P, version 2.0) Biometric Research, New York State Psychiatric Institute, New York, NY.

Fukagawa, K., Sakata, T., Shiraishi, T., Yoshimatsu, H., Fujimoto, K., Ookuma, K., 1989. Neuronal histamine modulates feeding behavior through H1-receptor in rat hypothalamus. Am. J. Physiol. 256, R605–R611.

Guy, W., 1976. ECDU Assessment Manual for Psychopharmacology. Revised. Department of Health Education and Welfare Publication (ADM) 76-338. National Institute of Mental Health, Rockville, MD, pp. 534–537.

Kaminsky, R., Moriarty, T.M., Bodine, J., Wolf, D.E., Davidson, M., 1990. Effect of famotidine on deficit symptoms of schizophrenia. Lancet 335 (8701), 1351–1352.

Kinon, M.J., Basson, B.R., Tollefson, G.D., 2000. Effect of long-term olanzapine treatment on weight change in schizophrenia. Schizophr. Res. 41 (Suppl. 1), B54.

Kroeze, W.K., Hufeisenn, S.J., Popadak, B.A., Renock, S.M., Steiberg, S.A., Ernsberger, P., Jayathilake, K., Meltzer, H.Y., Roth, B.L., 2003. H1- histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacology 28, 519–526.

Langtry, H.D., Grant, S.M., Goa, K.L., 1989. Famotidine. An updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in peptic ulcer disease and other allied diseases. Drugs 38, 551–590.

Masaki, T., Yoshimatsu, H., Chiba, S., Watanabe, T., Sakata, T., 2001. Targeted disruption of histamine H1-receptor attenuates regulatory effects of leptin on feeding, adiposity, and UCP family in mice. Diabetes 50, 285–391.

Potenza, M.N., Holmes, J.P., Kanes, S.J., McDougle, C.J., 1999. Olanzapine treatment of children, adolescents and adults with pervasive developmental disorder: open-label pilot study. J. Clin. Psychopharmacol. 19, 37–44.

Poyurovsky, M., Pashinian, A., Gil-Ad, I., Maayan, R., Schneidman, M., Fuchs, C., Weizman, A., 2002. Olanzapine-induced weight gain in patients with first-episode schizophrenia: a double-blind, placebo-controlled study of fluoxetine addition. Am. J. Psychiatry 159, 1058–1060.

Poyurovsky, M., Isaacs, I., Fuchs, C., Schneidman, M., Faragian, S., Weizman, R., Weizman, A., 2003. Attenuation of olanzapine-induced weight gain with reboxetine in patients with schizophrenia: a double-blind, placebo-controlled study. Am. J. Psychiatry 160, 297–302.

Prell, G.D., Rosse, R.B., Deutsch, S.I., 1996. Apparent absence of famotidine-antipsychotic drug interactions in patients with chronic schizophrenia. J. Psychiatry Neurosci. 21, 61–62.

Rosse, R.B., Kendrick, K., Fay-McCarthy, M., Prell, G.D., Rosenberg, P., Trui, L.C., Wyatt, R.J., Deutsch, S.I., 1996. An open-label study of the therapeutic efficacy of high-dose famotidine adjuvant pharmacotherapy in schizophrenia: preliminary evidence for treatment efficacy. Clin. Neuropharmacol. 19, 341–348.

Sacchetti, E., Guarneri, L., Bravi, D., 2000. H2 antagonist nizatidine may

control olanzapine-associated weight gain in schizophrenic patients. Biol. Psychiatry 48, 167–168.

Simpson, G.M., Angus, J.W.S., 1970. A rating scale for extrapyramidal side effects. Acta Psychiatr. Scand. 212, 11–19 (Suppl.).

Stoa-Birketvedt, G., 1993. Effect of cimetidine suspension on appetite and weight in overweight subjects. Br. Med. J. 30 (6885), 1091–1093.

Stoa-Birketvedt, G., Lovhaug, N., Vonen, B., Florholmen, J., 1997. H2-receptor antagonist reduces food intake and weight gain in rats by non-gastric acid secretory mechanisms. Acta Physiol. Scand. 161, 489–494.

Stoa-Birketvedt, G., Paus, P.N., Ganss, R., Ingebretsen, O.C., Florholmen, J., 1998. Cimetidine reduces weight and improves metabolic control in overweight patients with type 2 diabetes. Int. J. Obes. Relat. Metab. Disord. 22, 1041–1045.

ORIGINAL ARTICLE

Weight gain management in patients with schizophrenia during treatment with olanzapine in association with nizatidine

Manejo do ganho de peso em pacientes portadores de esquizofrenia durante o tratamento com olanzapina em associação com nizatidina

Sheila Seleri Marques Assunção,[1] Sandra Inês Ruschel,[2,3,4] Lucena de Cássia Rodrigues Rosa,[5] João Alberto O Campos,[6] Mercedes Jurema O Alves,[7,8,9,10,11] Oswaldo Luis Bracco,[12] Mauricio Silva de Lima[12,13,14]

Abstract

Objective: Weight gain is associated with treatment with many psychotropic agents. Nizatidine, H2 receptor antagonist, has been proposed to have weight-reducing effects. This was a 12-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of nizatidine in reducing/limiting weight gain in patients with schizophrenia who have been under treatment with olanzapine. Method: Patients receiving olanzapine (2 to 6 months) and weight gain ≥ 5% of their body weight during olanzapine treatment were randomly assigned to receive nizatidine 600 mg or placebo for up to 12 weeks. Change in psychopathology was assessed using Brief Psychiatric Rating Scale scores from baseline to endpoint. Safety was assessed using the Safety Assessed Software, assessment of glucose and lipid blood levels, and treatment-emergent adverse events. Results: Out of 54 patients enrolled in this analysis, 45 completed the protocol. The mean weight change prior randomization was 7.6 kg and 7.3 kg for those randomized to placebo and nizatidine, respectively (p = 0.828). Patients receiving placebo and nizatidine had a mean weight gain of 12.3% (0.7 kg) and 12% (1.1 kg) from baseline to endpoint, respectively (p = 0.9). Patients from both groups experienced a statistically significant decrease on the Brief Psychiatric Rating Scale mean score from baseline to endpoint. Treatment-emergent adverse events were reported by 18.5% and 25.9% on the placebo and nizatidine group, respectively. There were no statistically significant differences in glucose and lipid blood levels from baseline to endpoint and between groups. Conclusions: The concomitant use of olanzapine with nizatidine was not effective in controlling weight gain in patients who had previously gained weight during treatment with olanzapine when compared to placebo.

Descriptors: Schizophrenia; Antipsychotics agents; Weight gain; Clozapine; Nizatidine

Resumo

Objetivo: Ganho de peso está associado ao tratamento com inúmeros psicotrópicos. O uso de nizatidina, um antagonista H2, pode estar associado à redução de peso. Este foi um ensaio clínico aleatorizado, duplo-cego, controlado com placebo, de 12 semanas, desenhado para avaliar a eficácia da nizatidina em reduzir/limitar o ganho de peso em pacientes com esquizofrenia recebendo olanzapina. Método: Pacientes recebendo olanzapina (entre dois e seis meses) e com ganho de peso ≥ que 5% desde o início do tratamento foram aleatorizados para receber nizatidina 600 mg ou placebo. Alterações psicopatológicas foram avaliadas usando-se a Brief Psychiatric Rating Scale *total. A segurança foi avaliada por meio da pontuação na* Safety Assessed Software*, avaliação dos valores de glicemia e lipídios e a incidência de eventos adversos decorrentes do tratamento. Resultados: Dos 54 pacientes incluídos na análise, 45 completaram o protocolo. A alteração média de peso antes da aleatorização foi de 7,6 kg e 7,3 kg nos pacientes aleatorizados para placebo e nizatidina, respectivamente (p = 0,828). Pacientes recebendo placebo e nizatidina tiveram, respectivamente, ganho médio de peso de 12,3% (7 kg) e 12% (1,1 kg) ao longo do estudo (p = 0,9). Ambos os grupos apresentaram diminuição estatisticamente significativa na pontuação média da* Brief Psychiatric Rating Scale*. Eventos adversos emergentes do tratamento foram relatados por 18,5% e 25,9% dos pacientes recebendo placebo e nizatidina, respectivamente. Não houve diferença estatisticamente significativa nos níveis glicêmicos e lipídicos do início ao final do estudo ou entre os grupos de tratamento. Conclusões: Comparado ao placebo, o uso concomitante de olanzapina e nizatidina não foi eficaz em controlar o peso em pacientes com ganho prévio de peso durante o tratamento com olanzapina.*

Descritores: Esquizofrenia; Agentes antipsicóticos; Ganho de peso; Clozapina; Nizatidina

[1] Bristol Meyers USA, USA [2] Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro (RJ), Brazil [3] Hospital Mário Kröeff, Rio de Janeiro (RJ), Brazil [4] Escola de Medicina Souza Marques, Rio de Janeiro (RJ), Brazil [5] Clínica Santa Mônica, Aparecida de Goiânia (GO), Brazil [6] Institute of Neuropsychiatry of the State of Goiás, Medical School, Universidade Federal de Goiás (Ufg), Goiânia (GO), Brazil [7] Academic Psychiatric Association of Minas Gerais [8] Psychiatric Association of Minas Gerais [9] Brazilian Society of Burns [10] Trauma League of Minas Gerais [11] Faculdade de Ciências Médicas de Minas Gerais (FCM/MG, School of Medical Sciences of Minas Gerais), Belo Horizonte (MG), Brazil [12] Eli Lilly do Brasil, Brazil [13] Universidade Federal de Pelotas (UFPel), Pelotas (RS), Brazil [14] Universidade Católica de Pelotas (UCPel), Pelotas (RS), Brazil

Financing: This clinical trial was sponsored by Eli Lilly do Brasil Ltda
Conflict of Interests: Dr. Sheila Seleri Marques Assunção worked for the company by the time the study was being conducted. Maurício Silva de Lima and Oswaldo Bracco are Lilly employees.
Submitted: September 5, 2005
Accepted: July 21, 2006

Correspondence
Maurício Silva de Lima
Eli Lilly do Brasil
Avenida Morumbi, 8264 - Brooklin
04703-002 São Paulo, SP Brasil
Phone: (55 11) 5535- 8112 Fax: (55 11) 5532-6994
E-mail: lima_Mauricio_silva_de@lilly.com

Introduction

According to the mental health supplement of the National Health Interview Survey,[1] body mass index (BMI) distribution of schizophrenic individuals is generally similar to or higher than that of the general population, and weight changes in schizophrenic patients were well documented even in the pre-antipsychotic drug era.[2] The reported prevalence of overweight and obesity in patients with schizophrenia has been found to range from 40% to 62%,[3-7] and obesity is a complicating factor in many medical illnesses commonly seen in patients with schizophrenia.[8-9] Atypical antipsychotics are associated with superior tolerability, compliance, and relapse prevention and have led to improved treatment for patients with serious mental illness.[10] However, novel antipsychotics apparently produce an even greater weight gain when compared to typical agents.[11-13] A recent meta-analysis of over 80 studies on weight change during antipsychotic treatment showed a mean weight gain after 10 weeks of treatment of 9.8 lb (4.45 kg) with clozapine, 9.1 lb (4.15 kg) with olanzapine, and 4.6 lb (2.10 kg) with risperidone compared to 2.4 lb (1.08 kg) with the typical antipsychotic haloperidol.[11] Many theories (including increased food intake[14-15] have been advanced to explain the antipsychotic-related weight gain in schizophrenia.[16-17] Recently, serotonin, dopamine, and histamine receptor blockade has been implicated.[18-19] In this manuscript, it is of particular interest the role of histamine in the regulation of appetite and satiety as it is well known that atypical antipsychotics have a much greater affinity to the H-1 receptor when compared to typical medications.[20] This fact is consistent with the hypothesis that effects on histamine may contribute to atypical antipsychotic-treatment associated weight gain. Cimetidine, an H-2 receptor antagonist, has been reported to reduce weight in overweighed healthy subjects,[21] and also in overweighed type 2 diabetes mellitus patients,[22] although this finding has not been unequivocal.[23-24] Gastrointestinal regulatory peptides, such as cholecystokinin, have been proposed to mediate the satiety signal from gut to brain. In normal subjects, cimetidine increased the basal cholecystokinin and may be one mechanism by which it reduces the appetite. A report by Sacchetti et al. described a patient with repeated episodes of weight gain during olanzapine treatment who experienced weight reduction after 4 to 5 weeks of therapy with nizatidine (150 mg BID), an H-2 antagonist.[25] In a 16-week double-blind trial, Cavazzoni et al. reported significantly less weight gain at weeks 3 and 4 with olanzapine+nizatidine 300 mg BID compared to olanzapine+placebo, although no statistical difference between groups was seen at 16 weeks.[26] In that study, nizatidine was well-tolerated and did not adversely affect clinical outcomes. In an open-label study, Lopez-Mato et al. described that ranitidine also prevented or corrected weight gain in patients receiving olanzapine.[27]

The studies by Cavazzoni et al. and Lopez-Mato et al. showed that H2 antagonists may prevent or reduce weight gain when initiated concomitantly with olanzapine treatment.[26-27] During the treatment with olanzapine, approximately 25% of schizophrenic patients has a decrease in body weight or gain no weight.[28] In those individuals, a pharmacological approach to control weight gain is certainly not recommended. According to a review by Kinon et al., approximately 48% of olanzapine-treated patients gain less than 7%.[28] For these patients, behavioral and dietary changes may suffice to manage their body weight changes and no pharmacological approaches would be necessary.[28]

The purpose of the present study was to evaluate whether the use of an H2 antagonist in schizophrenic patients who have already gained weight could promote stabilization or reduction in body weight. Additionally, patients were considered responders if remained in therapy for 6 weeks or more and had no weight gain or a weight gain ≤ 3% since started using nizatidine (baseline). Non-responders were defined as any patients who failed to remain at least 6 weeks in the study and had gained > 3% since starting treatment with nizatidine. Possible effects of nizatidine on psychopathology and safety parameters were also assessed.

Method

1. Sample

Outpatient subjects (male or female, 18 to 65 years of age) met DSM-IV[29] diagnostic criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder. After a complete description of the study to the subjects, written informed consent was obtained. In order to be eligible to participate in this protocol, patients had to be in treatment with olanzapine (5 to 20 mg/day) for no less than 2 months and no more than 6 months, had a record of their body weight when initiated on olanzapine, had gained ≥ 5% since initiated the treatment with olanzapine, and had a total BPRS score < 45. Patients were excluded if they had any known physical illness that could affect body weight and composition, were currently participating in a formal weight loss program, or had a body mass index (BMI) ≥ 40 kg/m^2 or weight ≥ 114 kg. Patients with a diagnosis of diabetes mellitus could be enrolled provided their condition was under control and if they were in treatment for DM for at least 6 months. The study protocol was approved by Hospital Mario Kroëff Ethical Review Board on the 28th November 2002.

2. Study design

This was a randomized, double-blind, 12-week placebo-controlled trial. After a complete description of the study to the subjects, written informed consent was obtained. After baseline assessments, all eligible patients were randomized to receive placebo (PBO) or 300 mg nizatidine BID (NIZ). This study had a total of 4 follow-up interviews and assessments were performed in a monthly basis. Figure 1 shows the study design.

3. Assessments

Patients were weighed at each visit. All investigators were given detailed instruction at study start-up on uniform and consistent weight measurements. Psychopathology was assessed using the total score of the 18-item Brief Psychiatric Rating Scale (BPRS; each item rated from 1 to 7).[30] Safety parameters were assessed by treatment-emergent adverse events, routine laboratory analytes, and extrapyramidal symptoms (EPS), measured by the total score of the Simpson–Angus Scale.[31] Treatment-emergent adverse events were considered those that worsened or were described for the first time after initiating the treatment with nizatidine.

4. Statistical analysis

A mixed-effects model for repeated measures analysis of variance (ANOVA) was used to analyze the primary outcome measure (i.e. mean changes in total body weight from baseline to endpoint) and other continuous data. When the distribution was not normal, it was used the Mann-Whitney non-parametric test. For the comparison between responders and non-

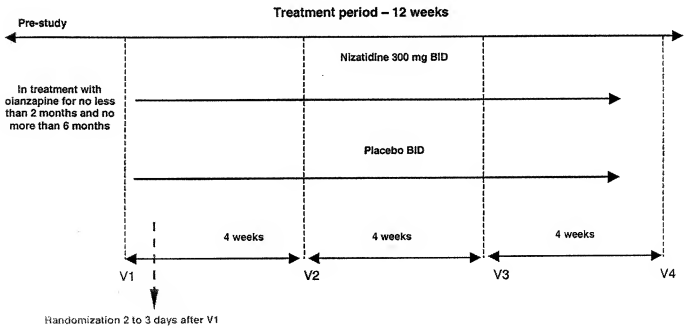


Figure 1 - Study design

responders, it was used the chi-square test. Results are expressed as the mean ± standard deviation (SD), unless otherwise stated. Statistical significance was set at $p \leq 5$.

Results

1. Sociodemographic and clinical characteristics

A total of 54 patients were included in this analysis; 27 patients were randomized to receive nizatidine 300 mg BID and 27 to receive placebo, in association with their usual treatment with olanzapine (5-20 mg/day). Forty-five patients completed the treatment with no statistical difference between completers in both groups ($p = 0.39$). Age at first episode, number of previous episodes and hospitalizations during the last 6 months were assessed and groups were comparable regarding those clinical characteristics at baseline (Table 1). Additionally, the groups did not differ in terms of socio-demographic characteristics (Table 1). Out of the total sample, 59.3% (n = 32) were male and the mean age was 35.2 (SD ± 12.2).

Patients had to have an increase of at least 5% in their body weight from the time they initiated on olanzapine and were randomized. There was no statistical difference in the mean percentage of weight gain before randomization to PBO or NIZ (PBO = 12.3%, NIZ = 12%) ($p = 0.829$). Table 2 shows body weight mean values before and during the study. The mean duration on olanzapine treatment, before being randomized to nizatidine or placebo, was 2.9 months for both groups. Among the 54 patients included in the analysis, none had a previous diagnosis of diabetes and none developed DM during the 12-week period of the study.

There were no statistical or clinical significant differences between genders. From the baseline assessment females had a 12.5% increase in body weight after the beginning of olanzapine treatment and males 11.9%, with BMC of 26.0 and 26.3 for females and males, respectively.

2. Effect on weight

Both groups did not significantly differ with respect to amount of weight gain at endpoint: patients receiving NIZ had a mean weight gain of 1.1 kg and those randomized to PBO gained 0.7 kg ($p = 0.9$). Figure 2 shows the change in body weight between groups. Multiples comparisons along treatment visits,

Table 1 - Sociodemographic and clinical characteristics at baseline for both treatment groups

		Placebo	Nizatidine	Total	P-value
Mean age (SD) – years		34.9 (12.2)	35.5 (12.4)	35.2 (12.2)	0.45
Gender (n/%)	Female	13 (48.1%)	9 (33.3%)	22 (40.7%)	0.27
	Male	14 (51.9%)	18 (66.7%)	32 (59.3%)	
Ethnicity (n/%)	White	16 (59.3%)	20 (74.1%)	36 (66.7%)	0.45
	Black/ mulatto	9 (33.3%)	5 (18.5%)	14 (25.9%)	
	Other	2 (7.4%)	2 (7.4%)	4 (7.4%)	
Body weight when initiating treatment with olanzapine (kg; SD)		64.3 (12.2)	64.8 kg (13.4)	64.5 (12.7)	0.76
Mean time between time initiating on OLZ and baseline (months)		2.9 (1.1)	2.9 (1.2)	2.9 (1.1)	0.67
Age at first episode (years; SD)		24.9 (8.4)	22.3 (6.4)	23.6 (7.5)	0.21
Mean number of previous episodes (SD)		4.7 (5.0)	3.2 (4.3)	4.0 (4.7)	0.12
Hospitalization during the last 6 months	Yes	15 (55.6%)	9 (33.3%)	24 (44.4%)	0.23
	No	12 (44.4%)	18 (66.7%)	30 (55.6%)	

Table 2 - Body weight measures at different points during the treatment with olanzapine

	Mean body weight when initiating treatment with olanzapine	Mean weight change between initiating treatment with olanzapine and visit 1	Mean weight change in patients with ≤2 months of treatment with olanzapine and visit 1	Mean weight change in patients with > 2 months of treatment with olanzapine and visit 1	% of weight change since initiating treatment with olanzapine and visit 1
PBO	64.8 kg (SD ± 13.4)	7.6kg (SD ± 3.7)	6.5 (SD ± 3.5)	8.7 (SD ± 3.8)	12.3% (SD ± 6.9%)
NIZ	64.3kg (SD ± 12.2)	7.3 kg (SD ± 4.0)	6.8 (SD ± 3.8)	7.8 (SD ± 4.2)	12% (SD ± 7.5%)
p-value NIZ vs. PBO	0.76	0.828	0.76	0.76	0.829

regardless of treatment groups, showed that body weight at endpoint was statistically, although not clinically (< 5%), higher when compared to baseline (V1 *versus* V4: p = 0.002); however, body weight at endpoint was significantly lower when compared to those at Visits 2 and 3 (V2 *versus* V4: p = 0.003, and V3 *versus* V4: p = 0.001).

3. Responders and non-responders

53.8% (n = 28) were considered responders, i.e., remained in therapy for at least 6 weeks and had no weight gain or had weight gain ≤ 3% since started using nizatidine (baseline). There was no statistical difference in the rates of responders for nizatidine 57.7% and placebo 50% (p = 0.58). Females had a lower responder rate (39.3%), when compared to males (60.7%), but this difference was not statistically significant (p = 0.63)

4. Effect on psychopathology and safety

Significant improvement on the BPRS total scores was observed in both treatment groups from baseline to endpoint (p < 0.001 for both groups). However, the BPRS score was not significantly different between groups at endpoint (PBO: 23.7 ± 9.9; NIZ: 24.2 ± 8.5; p = 0.12). Figure 3 shows the changes in BPRS total score from baseline to endpoint in both groups. Decreases in BPRS total score were seen as early as week 4 (V1- NIZ: 27.5; PBO: 23.9 vs. V2 - NIZ: 25.4; PBO: 21.8; p = 0.006)

All patients showed a statistically significant improvement on the Simpson–Angus Scale from baseline to endpoint (p < 0.001). There were no statistically significant differences between groups at endpoint (PBO: 1.4 ± 2.8; NIZ: 0.6 ± 1.3; p = 0.51). There were no significant differences in treatment-emergent adverse events reported between groups (NIZ: 25.9% *versus* PBO: 18.5%; p = 0.5), and only 3 patients (1 NIZ; 2 PBO) discontinued the study due to an adverse event. Headache, somnolence, and hypersomnia were the only treatment-emergent adverse events reported by more than 2 patients. There were no significant differences between groups on any of the measured laboratory analyses (Table 3).

Discussion

The appropriate selection of APs ought to be based on drug efficacy and risk factors in clinical daily practice. Although more efficacious in a number of clinical outcomes, treatment with atypical antipsychotics may be associated with weight gain.[11-13] Thus, patients should be informed of that adverse event in order to avoid excessive weight gain. Nutritional advice must be given and regular physical exercise recommended. Many studies have shown that behavioral, pharmacological or a combination of both methods turned out to be efficacious in preventing weight gain.[13,26,32]

At present, there is no standardized pharmacological treatment for antipsychotic-related body weight gain. Some studies have assessed the effects of agents such as amantadine, orlistat,

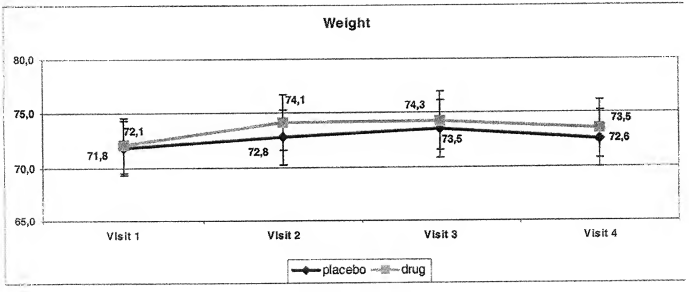


Figure 2 - Body weight changes from baseline to endpoint in patients receiving nizatidine or placebo

Table 3 - Laboratory analytes between treatment groups and from baseline to endpoint

	V1 (week 0)	V4 (week 12)	p-value NIZ vs. PBO	p-value V1 vs. V4
Glicemia			0.414	0.606
PBO	83.3 (10.2)	84.6 (14.7)		
NIZ	85.4 (12.0)	87.1 (14.5)		
Cholesterol total			0.241	0.630
PBO	191.3 (36.8)	180.3 (34.1)		
NIZ	195.5 (47.0)	198.8 (46)		
HDL			0.8	0.9
PBO	49.2 (9.4)	46.5 (12.7)		
NIZ	48.7 (13.4)	45.8 (10.6)		
LDL			0.34	0.77
PBO	191.3 (36.8)	180.3 (34.1)		
NIZ	195.5 (47.0)	198.8 (46.0)		
Triglycerides			0.38	0.28
PBO	148.2 (71.0)	152.7 (75.1)		
NIZ	168.4 (120.0)	179.4 (112.7)		

metformin, nizatidine, and topiramate as pharmacological alternatives to manage this adverse event.[26,33-37] Treating weight gain with pharmacological agents in psychiatric patients must be done with caution as some drugs used to this purpose may exacerbate the psychiatric condition, once their primary site of action is the central nervous system.[12] Thus, the use of a medication to manage weight gain in psychiatric patients without central activity would be of particular interest.[12]

Previous studies showed that H2 antagonists might be related to weight loss in humans.[21-22,25-27] Causing weight loss by a mechanism that is yet to be defined, H2 antagonists are more likely to have their the primary site of action outside the central nervous system, as H-2 antagonists as a class are very hydrophilic and cross the blood–brain barrier to a limited extent.[28] Due to their peripheral site of action, H2 antagonists were used in some studies to manage weight gain in schizophrenic patients on olanzapine. Among those studies two are of most interest due to their design and methodology.[26-27]

Cavazzoni et al. compared two different doses of nizatidine (300 mg QD and 300 mg BID) with placebo to manage weight gain in patients initiating treatment with olanzapine.[26] At weeks 3 and 4, patients treated with nizatidine 300 mg BID reported significantly less weight gain compared to placebo; however, no significant difference between the treatment groups was seen at 16 weeks. The authors suggested that nizatidine 300 mg BID may have a potential effect, albeit transient and possibly dose-related. The authors hypothesized a rebound phenomenon of weight recovery, a decrease in compliance over time, and interindividual variability as possible reasons for the apparent lack of persistent effect of nizatidine in controlling weight gain.

Lopez-Mato et al. evaluated the efficacy of different doses of ranitidine in preventing or reducing weight gain in schizophrenic patients treated with olanzapine in an open-label trial.[27] According to their results, the use of ranitidine prevented or corrected weight gain in 59.6% of the patients receiving olanzapine. Patients not receiving ranitidine exhibited an average weight gain of 3.4 kilograms (SD: -2.5 to +16 kg), and an increase of 1.19 kg/m² in their BMI. Patients treated with ranitidine 300 mg/day gained 0.9 kilogram (SD: -4 and +10.6 kg), with an increase of 0.34 kg/m² in their BMI. For patients on the highest dose of ranitidine (600 mg), the weight gain curve trended towards normalization. They lost 1.6 kilogram and 0.6 points in their BMI, in average. Additionally, they lost up to –15 kilograms and gained less weight (up to 7 kilograms) when compared to those receiving a lower dose of ranitidine or placebo. Contrary to the study of nizatidine by Cavazzoni et al. the effect of weight control with ranitidine was sustained along all the study period.[26]

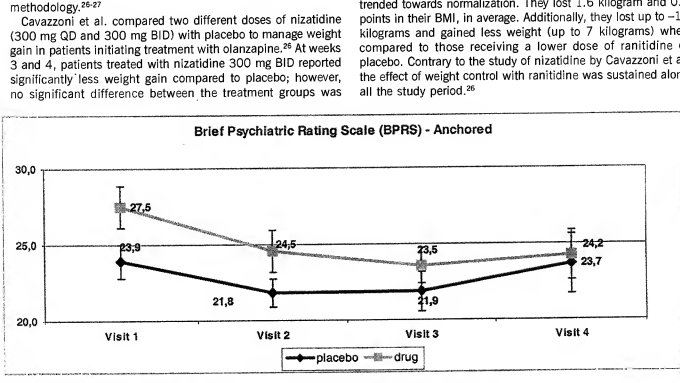


Figure 3 - Changes in BPRS total score from baseline to endpoint according to treatment groups

Our study had the main objective of assessing whether an H2 antagonist, nizatidine, could be of help for patients with schizophrenia or related disorders that had already had substantial weight gain (≥ 5%) with olanzapine. If so, it would avoid unnecessary use of this pharmacological strategy to a significant part of patients who, during the course of their treatment with olanzapine, did not present weight gain nor had a weight gain that could be managed by behavioral and/or dietary strategies.[28]

We demonstrated that nizatidine when administered to olanzapine-treated patients with previous weight gain did not differ from placebo in the amount of weight control. It could be hypothesized that the greater increases in body weight occurred most likely during the first months after initiating treatment with olanzapine (pre-study). Patients randomized to nizatidine gained on average 6.8 kg and those randomized to placebo, 6.5 kg, during that study period. Although continuing gaining weight, this increase was substantially lower (NIZ: 1.1kg and PBO: 0.7 kg) when compared to the initial phase of treatment with olanzapine. Those results are in accordance with previously published data, showing that the rate of weight gain appears to be more intense during the first 12 weeks of olanzapine treatment, occurring less rapidly in subsequent weeks, and plateauing around the 39th week.[28] That might be one explanation why nizatidine did not differ from placebo in controlling weight as most patients could already be in or close to the plateau phase.

Another concern related to the use of atypical antipsychotics is the potentially increased risk of treatment-emergent diabetes. Contrary to weight gain, that has been reported with some atypicals more than others (e.g., clozapine, olanzapine), recent reviews show that the potentially increased risk of DM appears to be a class-wide occurrence among the new generation antipsychotics.[13,39] In our study, blood glucose and lipids levels did not differ from baseline to endpoint and between patients in the two treatment groups during the 12 weeks of the study duration.

There are consistent data suggesting that the main driver when choosing an antipsychotic treatment must be the drug efficacy.[13,39] Although treated as a homogeneous group, effectiveness is different from one drug to another. For instance, in a recent meta-analysis, Davis et al. described that only clozapine, amisulpride, risperidone, and olanzapine were more efficacious than typicals, while other atypicals were not. After considering the drug's efficacy, medication's risk profile must also be considered.[10]

According to measures in the levels of psychopathology, extrapyramidal symptoms, laboratory analytes, and reports of treatment-emergent adverse events assessed during the study, nizatidine did not interfere with the efficacy and/or safety of olanzapine. This study did not have the intention to determine the efficacy or safety of olanzapine. Patients' levels of psychopathology were followed-up in the trial by using BPRS. Patients included in this study were not in an acute phase due to the inclusion criterion of a score on the total BPRS < 20. Despite this low score at baseline, it is interesting to note that patients using olanzapine continued to show a slight, yet statistically significant, decrease in their level of psychopathology during the 12 weeks of the study duration. Furthermore, extrapyramidal symptoms also decreased in intensity, according to score at Simpson-Angus Scale.

1. Study limitations

This study has some limitations that must be considered. It could be argued that this sample size is not large enough to detect differences between treatment groups. However, this may not be the main reason for these negative findings. There is some limitation in the design of the study. Before entering the study, patients were receiving olanzapine according to their physicians' discretion, as they were not in a controlled trial. Thus, the exact doses and compliance to the antipsychotic treatment might have substantially diverged among patients. Furthermore, patients in this study gained on average 7 kg after starting taking Olanzapine and before entering the trial. One could hypothesize that if nizatidine was delivered earlier before weight gain, during the first weeks of treatment, results might have favored this intervention.

Finally, only body weight at the time olanzapine was initiated was a required measure to be enrolled in this study, yet no requirement was made regarding metabolic parameters. Any conclusion about changes in those analyses must be taken very cautiously. The same caution must be observed regarding conclusions on psychopathology and extrapyramidal symptoms, as the study was not designed for purposes of efficacy and/or safety.

Conclusions

Our results showed that, when patients had already gained substantial weight with olanzapine treatment, the concomitant use of nizatidine did not differ from placebo in controlling weight gain. Olanzapine shows a remarkable efficacy in improving psychopathology in schizophrenic patients; however, some patients may experience significant weight gain. Innumerous studies show that weight gain can be adequately and successfully managed with behavioral and/or pharmacological approaches. The relatively rapid onset of weight gain with olanzapine suggests the importance of early intervention for weight gain mitigation. Proactive interventions to deal with this adverse event, regardless of the nature of the intervention, may result in weight stabilization/loss. Furthermore, appropriate attention to this issue can improve the quality of life for patients treated with antipsychotic drugs, and decrease morbidity and mortality due to weight-related disorders.

References

1. Center for Diseases Control (CDC). National Health Interview Surveys (NHIS). U.S. Department of Health and Human Services (USDHHS): [cited 15 Jan 2006]1989. CD-ROM. Series 1993;10(3). Available at: http//cdc.gov/nchs/about/major/nhisquest_data_related_1969_1996.htm .
2. Post F. Body-weight changes in psychiatric illness: a critical survey of the literature. *J Psychosom Res*. 1956;1(3):219-26.
3. Allison DB, Fontaine KR, Heo M, Mentore JL, Cappelleri JC, Chandler LP, Weiden PJ, Cheskin LJ. The distribution of body mass index among individuals with and without schizophrenia. *J Clin Psychiatry*. 1999;60(4):215-20.
4. Silverstone T, Smith G, Goodall E. Prevalence of obesity in patients receiving depot antipsychotics. *Br J Psychol*. 1988;153:214-7.
5. Stedman T, Welham J. The distribution of adipose tissue in female inpatients receiving psychotropic drugs. *Br J Psychiatry*. 1993;162:249-50.
6. Kendrick T. Cardiovascular and respiratory risk factors and symptoms among general practice patients with long-term mental illness. *Br J Psychiatry*. 1996;169(6):733-9.
7. Centorrino F, Baldessarini RJ, Kando JC, Frankenburg FR, Vopicelli SA, Flood JG. Clozapine and metabolites: concentrations in serum and clinical findings during treatment of chronically psychotic patients. *J Clin Psychopharmacol*. 1994;14(2):119-25.

8. Wirshing DA, Spellberg BJ, Erhart SM, Marder SR, Wirshing WC. Novel antipsychotics and new onset diabetes. *Biol Psychiatry*. 1998;44(8):778-83.
9. Masand PS, Blackburn GL, Ganguli R, Goldman LS, Gorman J, Greenberg I, Kawachi I, Perkins DO, Sach CS. Weight gain associated with the use of antipsychotic medications. *J Clin Psychiatry Audiograph Series*. 1999;2.
10. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry*. 2003;60(6):553-64.
11. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 1999;156(11):1686-96.
12. Green AI, Patel JK, Golsman RM, Allison DB, Blackburn G. Weight gain from novel antipsychotic drugs: need for action. *Gen Hosp Psychiatry*. 2000;22(4):224-35.
13. Marder SR, Essock SM, Miller AL, Buchanan RW, Casey DE, Davis JM, Kane JM, Lieberman JA, Schooler NR, Covell N, Stroup S, Weissman EM, Wirshing DA, Hall CS, Pogach L, Pi-Sunyer X, Bigger JT Jr, Friedman A, Kleinberg D, Yevich SJ, Davis B, Shon S. Physical health monitoring of patients with schizophrenia. *Am J Psychiatry*. 2004;161(8):1334-49.
14. Bromel T, Blum WF, Ziegler A, Schulz E, Bender M, Fleischhaker C, Remschmidt H, Krieg JC, Hebebrand J. Serum leptin levels increase rapidly after initiation of clozapine therapy. *Mol Psychiatry*. 1998;3(1):76-80.
15. Robinson RG, McHugh PR, Folstein MF. Measurement of appetite disturbances in psychiatric disorders. *J Psychiatr Res*. 1975;12(1):59-68.
16. Doss FW. The effect of antipsychotic drugs on body weight: a retrospective review. *J Clin Psychiatry*. 1979;40(12):528-30.
17. Stanton JM. Weight gain associated with neuroleptic medication: a review. *Schizophr Bull*. 1995;21(3):463-72.
18. Wirshing DA, Wirshing WC, Kysar L, Berisford MA, Goldstein D, Pashdag J, Mintz J, Marder SR. Novel antipsychotics: comparison of weight gain liabilities. *J Clin Psychiatry*. 1999;60(6):358-63.
19. Cookson JC. Side effects during long-term treatment with a depot antipsychotic medication. *Clin Neuropharm*. 1991;14(Suppl 2):S24-S32.
20. Bymaster FP, Hemrick-Luecke SK, Perry KW, Fuller RW. Neurochemical evidence for antagonism by olanzapine of dopamine, serotonin, alpha 1-adrenergic and muscarinic receptors in vivo in rats. *Psychopharmacology* (Berlin). 1996;124(1-2):87-94.
21. Stoa-Birketvedt G. Effect of cimetidine suspension on appetite and weight in overweight subjects. *BMJ*. 1993,306(6885):1091-3.
22. Stoa-Birketvedt G, Paus PN, Garnes R, Ingebretsen OC, Florholmen J. Cimetidine reduces weight and improves metabolic control in overweight patients with type 2 diabetes. *Int J Obes Relat Metab Disord*. 1998 ;22(11):1041-5.
23. Andersen T, Hojby Rasmussen M. Cimetidine and obesity: conflicting evidence. *Int J Obes Relat Metab Disord*. 1999;23(5):550-1.
24. Birketvedt GS, Thom E, Bernersen B, Florholmen J. Combination of diet, exercise and intermittent treatment of cimetidine on body weight and maintenance of weight loss. A 42 months follow-up study. *Med Sci Monit*. 2000;6(4):699-703.
25. Sacchetti E, Guarneri L, Bravi D. H(2) antagonist nizatidine may control olanzapine-associated weight gain in schizophrenic patients. *Biol Psychiatry*. 2000;48(2):167-8.
26. Cavazzoni P, Tanaka Y, Roychowdhury SM, Breier A, Allison DB. Nizatidine for prevention of weight gain with olanzapine: a double-blind placebo-controlled trial. *Eur Neuropsychopharmacol*. 2003;13(2):81-5.
27. Lopez-Mato A, Rovner J, Illa G, Vieitez A, Boullosa O. Randomized, open label study on the use of ranitidine at different doses for the management of weight gain associated with olanzapine administration. *Vertex*. 2003;14(52):85-96.
28. Kinon BJ, Basson BR, Gilmore JA, Tollefson GD. Long-term olanzapine treatment: weight change and weight-related health factors in schizophrenia. *J Clin Psychiatry*. 2001;62(2):92-100.
29. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Association; 1994.
30. Woerner M, Mannuzza S, Kane J. Anchoring the BPRS: an aid to improve reliability. *Psychopharmachol Bull*. 1988;24(1):112-7.
31. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl*. 1970;212:11-9.
32. Vreeland B, Minsky S, Menza M, Rigassio Radler D, Roemheld-Hamm B, Stern R. A program for managing weight gain associated with atypical antipsychotics. *Psychiatr Serv*. 2003;54(8):1155-7.
33. Deberdt W, Winokur A, Cavazzoni PA, Trzaskoma QN, Carlson CD, Bymaster FP, Wiener K, Floris M Breier A. Amantadine for weight gain associated with olanzapine treatment. *Eur Neuropsychopharmacol*. 2005;15(1):13-21.
34. Baptista T, Kin NM, Beaulieu S, de Baptista EA. Obesity and related metabolic abnormalities during antipsychotic drug administration: mechanisms, management and research perspectives. *Pharmacopsychiatry*. 2002;35(6):205-19.
35. Morrison JA, Cottingham EM, Barton BA. Metformin for weight loss in pediatric patients taking psychotropic drugs. *Am J Psychiatry*. 2002;159(4):655-7.
36. Atmaca M, Kuloglu M, Tezcan E, Ustundag B, Kilic N. Nizatidine for the treatment of patients with quetiapine-induced weight gain. *Hum Psychopharmacol*. 2004;19(1):37-40.
37. Vieta E, Sanchez-Moreno J, Goikolea JM, Colom F, Martinez-Aran A, Benabarre A, Corbella B, Torrent C, Comes M, Reinares M, Brugue E. Effects on weight and outcome of long-term olanzapine-topiramate combination treatment in bipolar disorder. *J Clin Psychopharmacol*. 2004;24(4):374-8.
38. Brunton LL. Agents for control of gastric acidity and treatment of peptic ulcers. In: Gilman AG, Rall TW, Nies AS, Taylor P, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 8th ed. New York/St. Louis/San Francisco: McGraw-Hill Inc. p. 897-913.
39. Expert Group. "Schizophrenia and Diabetes 2003' Expert Consensus Meeting, Dublin, 3-4 October 2003: consensus summary. *Br J Psychiatry Suppl*. 2004;47:S112-4.